BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

Entered as Second-Class Matter at the Baltimore, Maryland, Postoffice

Vol. XXIX—No. 326] BALTIMORE, APRIL, 1918 [Price, 50 Cents

APR 8 1918

UNIV. OF MICH. LIBRARY

CONTENTS

PAGE

Cinq ans Après.
By F. C. Shattuck, M. D. 77

Diabetes: The Results of Past Treatment and Future Problems.
By Elliott P. Joslin, M. D. 80

A Study of An Autoagglutinin Occurring in a Human Serum. (Illustrated.)
By Mildred C. Clough, M. D., and Ina M. Richter, M. D. 86

A Simple Method for the Determination of Venous Pressure. (Illustrated.)
By N. Worth Brown, M. D. 93

Abstracts of Papers 94
The Maintenance Diet in Diabetes Mellitus as Determined by the Nitrogen Equilibrium [Herman O. Mosenthal and Samuel W. Clausen];—The Effect of Diet on Blood Sugar in Diabetes Mellitus. (Abstract.) [Herman O. Mosenthal, Samuel W. Clausen and Alma Hiller];—A Rare Type of Bladder Ulcer: Further Notes, With a Report of Eighteen Cases [Guy L. Hunner].

PAGE

Proceedings of Societies.
The Johns Hopkins Hospital Medical Society. 97
Exhibition of a Case of Psoriasis. (Illustrated.) [Dr. Lloyd W. Ketron];—The Use of Relaxation Incisions in Dealing With Extensive Unstable Scars [John Staige Davis];—Observations on Bird Malaria and the Pathogenesis of Relapse in Human Malaria [Lieut.-Colonel Eugene R. Whitmore];—The Preparation of the U. S. Army Triple Typhoid Vaccine. (Illustrated with Moving Pictures.) [Major C. G. Snow];—Recent Work on the Differentiation of the Paratyphoid Group in Relation to Disease in Man [Dr. Charles Krumwiede].

Books Received 99

CINQ ANS APRÈS[1]

By F. C. Shattuck, M. D., Boston, Mass.

Many a man has wished he might return to earth and note the changes since his demise. I have never been of that number, for is it not an endless chain? One return might merely whet the appetite for another, stimulating desire, the extinguishment of which, so the Buddhists hold, should be our one and constant aim. Or, what seems more likely, the return tripper might find himself hopelessly out of place, thoroughly wretched. Probably the existing plan is best. It would seem wise to accept it as such, inasmuch as we have no choice.

Absolutely without volition of my own, and without blame attaching to the all-highest Kaiser, if any credence can be given to his unwonted burst of modesty when he told us he did not will this war, I have been resurrected, and vouchsafed a glimpse of what five years can do in hospital medicine. The Kaiser has done his best to convince his people that nothing in the heavens above, in the earth beneath, or in the waters under the earth, takes place contrary to his will. I see it stated that he has been graciously pleased to ennoble God, who is henceforth entitled to enjoy the prefix von—von Gott.

In the spring of 1912, having reached the age limit then in force at the Massachusetts General Hospital, I was consigned to the tomb, and, indeed, was such a horrible example of dry rot—or something—that the age limit was promptly put down from 65 to 60. May I add that I think this a wise step, promotive of far more good than harm? The ancient adage says "a young man for action, an old man for counsel." A service in a modern hospital is surely a sphere of *action*, and an old man's counsel can always be had if wanted. It is well for those who are growing or have grown old, to read, from time to time, mark, learn, and inwardly digest, Kipling's poem on the old men, as salutary as some of it may be brutal.

The war came; then our entrance into it, and the depletion of hospital staffs for the United States service. Shorthandedness became acute, and it was deemed necessary to rob something, so the authorities at the Massachusetts General Hospital began by robbing the grave, holding the cradle in reserve for the present, and after five years of desuetude, I trust relatively innocuous, I found myself again in charge of a medical service in a hospital. Some of the changes I note after this interval, and some reflections thereupon form the subject of my short and informal talk to you this evening.

[1] Read before a meeting of The Johns Hopkins Hospital Medical Society, January 21, 1918.

One striking fact was the small number of typhoid cases. I think the number was diminishing while I was still active; but I could not help contrasting 5 per cent of medical beds occupied by typhoid patients with nearly 50 per cent as I have seen in Octobers of the past. Two of the cases in my service convey a lesson. They were a brother and an uncle of an Italian who was in the hospital in the summer with typhoid, but carried a bacilluria six weeks after recovery in other respects. He was reported to the Board of Health and by them put in another hospital where he stayed two weeks, then being discharged, as reported, with constant negative cultures. He went back and roomed with his brother and uncle, both of whom came down with typhoid. The original case re-entered the Massachusetts General Hospital and gave a positive culture. I had supposed hexamethylenamine to be truly specific for typhoid bacilluria, and, at the time of the Spanish war, I ordered the drug given as a routine thing to every case of typhoid. It seems, thus, that a few cases are resistant. The spread of typhoid through the urine of a carrier would seem a more insidious danger than through the feces, a more offensive excretion. The time seems near when it will be as hard to demonstrate a case of typhoid to students as it is now a case of smallpox. I was gratified to find that the liberal diet in typhoid, of which I was an early advocate, is still in force. What plan of diet you follow here I do not know, but McCrae in 1907 either had never heard of a liberal diet in typhoid or perhaps thought it too dangerous even to mention.

Peptic ulcer is my next theme. I was formerly quite accustomed to the nearly constant presence in my female ward of several cases of gastric ulcer, almost invariably with the clinching evidence of hemorrhage. These almost always did well under purely medical treatment unless there was distinct pyloric stenosis. I now find a decidedly larger number of cases in the male ward, often sent in for such study as the slender purse cannot afford outside of the hospital. The X-ray here occupies a more prominent position than it did, partly through improvements in methods, mainly through accumulated experience. Our X-ray expert, Dr. Holmes, holds the, to my thinking, sound view that X-ray evidence of ulceration in or about the upper digestive tract is corroborative rather than determinant. Its positive value is great when it fits in with evidence derived from the history, physical examination and other tests. Am I warranted in suspecting that some X-ray experts attach undue finality to their findings? Personally, when the X-ray and the other evidence diverge, I should put the X-ray in the second place. Let me mention two cases, among others, which come into my mind in which X-ray evidence would have been helpful. A young woman, not a bleeder either of congenital or any apparent acquired origin, had persistent hæmatemesis. I urged operation, which showed that the blood oozed from the whole gastric mucous membrane. Possibly an X-ray might have saved her from operation and from death.

A middle-aged woman was transferred from the surgical to my ward as inoperable. She had coffee-ground vomit, no free HCl and an epigastric tumor. We all concurred in the diagnosis of gastric cancer, and her friends were advised to take her home as speedily as possible to a neighboring state. Later I was told that she died of pneumonia several years after discharge from the hospital, and that an autopsy showed her epigastric tumor to be a displaced kidney.

Peptic ulcer still seems to me to belong to the physician with the surgeon in reserve. There can be no question as to the addition to our power of recognition of peptic ulcer afforded by the ante-mortem knife of the surgeon. You all remember Dr. Wendell Holmes' comparison of an autopsy to inspection of the fireworks the morning after the Fourth of July. Modern surgery has amplified our knowledge of the pathology of the living as nothing else could have done. At one time, 10 years ago, if you will, with the best intentions to keep an open mind, I felt that indiscriminate gastroduodenal surgery was in the ascendant, that surgery was too often regarded as a short cut to cure. I could not satisfy myself how gastroenterostomy could obviate the underlying cause of ulceration. Marked more or less temporary improvement might be accounted for by the rest which operation brought the patient and his stomach.

I recall the case of an unfortunate young woman in my service who had undergone at least two operations for dyspepsia in another hospital. She was ungrateful enough to be no better, and entered to find out whether another operation might restore the upper digestive channels as planned by the Divine Architect. Adhesions were separated, and the gastroenterostomy closed—with considerable relief up to the time of her discharge. It has been impossible to learn of the end result.

This year I got the impression that the surgical treatment of peptic ulcer is more discriminating than it was. My time and basis for judgment were too limited for more than an impression; but I can see no reason to change the conservative view I have long held on this point. The crucial test of time and the growth of "end result" statistics should put us in a better position to judge than was occupied five years ago. We are less patient than we used to be. We are in a hurry to "get results." And a clean surgeon rarely kills.

Am I dreaming when I think I recall that recognized cases of gastric ulcer were rare in the wards of this hospital 25 years ago? Tell me, Dr. Thayer.

Five years ago, with us at the Massachusetts General Hospital, at least, the fresh, cold air treatment of pneumonia was in full swing. A head-high screen around the bed of the pneumonic did something to temper the air from the open window to the other shorn lambs in the ward. In short, the open-air treatment was carried out as far as practicable in an open ward. This autumn the screen was still in evidence, the open window less so, as it seemed to me. Why then the screen?—I asked myself. The ordinary pneumonias are not easily contagious, and a patient who is either a menace or a real disturbance to others should not be in an open ward. Though asphyxia is rarely a potent factor in pneumonic death, I have long held, and used to teach that a plentiful supply of fresh air was desirable. The young and vigorous will stand, and possibly benefit by, a lower temperature than the old and feeble. The craving

of old people for warmth would seem to indicate an intolerance of cold, due in part, at least, to lessened activity or involution of the thyroid gland. Five years ago the studies of Cole and others on the varieties of the pneumococcus had not progressed far enough to help in prognosis or treatment. The routine effort to determine the type of pneumonia I noted as another innovation. Until some efficacious antidotal treatment for pneumonia is discovered, the mortality will remain about the same. Here may I express my great sympathy to you in the loss of Theodore Janeway? In his case surely death loved a shining mark.

A paper by Dr. Charles H. Lawrence and myself will appear shortly, analyzing the pneumonias at the Massachusetts General Hospital from 1889 to 1916, about 3500 in number. Our data begin where Townsend and Coolidge left off, and we find the mortality practically the same in the days of heroic, expectant and alcoholic, symptomatic, and fresh air treatment. I wonder whether the pendulum has not swung too far away from alcohol in cases of profound general sepsis. Many of us elders who have lived through the unquestioned abuse of alcohol in disease cannot get rid of the belief that there are cases of sepsis in which alcohol, even in massive doses, are life-saving, if given with brains. I emphasize brains, for the best results are to be obtained only under close and skilled observation. All trace of alcohol in the breath should disappear before more is given; so, also, any toxic effect, flushing, for instance. Fifty years from now will alcohol be considered always, everywhere, under all circumstances, the unmitigated poison which some present day apostles hold it to be; and which the American Medical Association has pronounced it to be? Fully realizing that what I may think cuts no ice, to use a colloquialism, I doubt. Mercury and bleeding were so abused that they fell into disuse, but have come back. I find that in 1912 in the Massachusetts Hospital $551.17 was spent for alcohol as an internal remedy against $133.36 in 1917. The whiskey bill in 1917 was 20 per cent larger than in 1912, but this probably indicates a rise in the price, not an increase in the amount. The following table may prove of interest:

	1908	1912	1917
Ale	$ 94.75	$174.97	$50.95
Beer	67.46	31.50	6.24
Brandy	114.75	131.62	....
Champagne	77.90	57.75	16.00
Wines	203.08	114.83	11.13
Whiskey	.....	40.50	49.04
	.....	$551.17	$133.36

The value of the X-ray in the detection of gall-stones has certainly increased in the past five years. This gain I am told is due to a shortening of the time of exposure from 20 seconds to a fraction of a second, thus reducing mobility of surrounding parts as a source of error.

To turn now from special diseases to the general trend of thought and practice in the past five years. I see real progress in the care and thoroughness with which the sick are studied, their histories and the course of their maladies recorded. Indeed, I found the records so voluminous and minute that it was hard to see the wood by reason of the trees. The labor of the chief of staff would be lightened and the mental training of the younger men promoted, as it seemed to me, by the addition of a brief, clear, logical, consecutive statement of the essentials of each case, especially the complicated ones. The power of terse statement with a quick eye for perspective and values is worth the labor of attainment. Are dictation and the typewriter enemies of prolixity and slovenliness in the use of our wonderful language? As an intimate knowledge of King James' Bible wanes, English decays.

As I look back 50 years when I began to frequent hospitals seriously, I note a wonderful advance in diagnostic and therapeutic procedure. The major part of this, certainly in importance, dates from the birth of bacteriology; chemistry, and some knowledge of the hitherto unknown vibrations, the X-rays among others, are also vital factors. When I began the study of medicine and for years thereafter we soon came to an end of our means of investigating disease as exemplified in a patient, and could devote much of our energies to caring for the sick man, a human being different from any other upon earth, and meriting study as a sick man, not merely as a case of disease. With the multiplication of instruments of precision, of chemical and other tests, psychological included, with the steady improvement in X-ray technique, the possibilities of study have grown many fold. The pace has not slackened these past five years, and some patients surely now have time to die or get well before a really scientific diagnosis is reached, and there is a greater chance for the patient to be forgotten in his disease. There is a possibility of error both in observation and in interpretation. This tendency, if it exists outside of my imagination, is enhanced by the polyglot publicum of our wards. The wall of language impedes some of the currents of human medicine. Some years ago I had a census made in my ward with 22 patients. There was only one I should call a Yankee, that term connoting to me a person of relatively pure New England blood. With many of these patients we can communicate only through an interpreter, not always at hand. Human fallibility constantly lurks behind even the instrument of precision and the chemical test.

I well remember an observation dropped by the shrewd and kindly, old, as he seemed to me then, Dr. Tessier of the Lyons Hôtel Dieu, 40 years ago—"Le médecin guérit rarement, améliore souvent, console toujours." To-day he cures oftener than he did then, for he knows far better what things are curable and how they are to be cured. He also relieves oftener. Does he as invariably and as surely console? There are still all too many cases in which consolation alone remains.

While I rejoice in and try to do justice to scientific progress, I should be sorry to think that any real values shrink or vanish. To slightly paraphrase a saying of our Lord—"Thus ought we to do but not to leave the other undone." I believe in the perfectibility of man—in time. It is surely in place—is it not?—to enter a plea for humanism on the scene where a great humanist scored so many of his triumphs, your and our William Osler.

DISCUSSION

Dr. W. S. Thayer (Abstract).—It was my rare good fortune nearly 30 years ago to come into my first service in the Massachusetts General Hospital under Dr. Shattuck, and it has been deeply interesting to me to hear what he had to say. He has mentioned various things that have interested me particularly.

In the first place, his observations on gastric ulcer. It is true that in 1890 when I first came here, for several years we had curiously few obvious gastric ulcers; whereas during the service of three months I had under Dr. Shattuck, we had a number of outspoken cases of these ulcers. Although we had few cases then, we have made up for it since. I think it was simply one of those remarkable periods during which we had a few cases come to us.

I was very much interested in what Dr. Shattuck had to say about sepsis. I confess to feeling very much as he does. I cannot believe that I have been absolutely deceived in the value of alcohol in some acute infections. When I was in the Massachusetts General, we were using alcohol quite freely. I remember one particular patient with pneumonia who was taking 36 oz. of whiskey a day. I was called up one night about midnight by the nurse, who said she was afraid something serious had happened. I hastened to the ward and found an individual with a perfectly normal temperature, sitting on the side of his bed and singing in the most ribald fashion. He had had his crisis and the alcohol was being continued! I should not be surprised if in after years we do not perhaps use a little more alcohol in acute infections than we are employing to-day.

It was nearly 30 years ago in the fall of 1888, when I came into the Massachusetts General and began my service with Dr. Shattuck. It was a most interesting and valuable service I had during that year. He was a good deal the sort of doctor that he has described to-night, if you read through what he said. He was not only a very acute clinician and a remarkably good observer, but he taught us how to treat patients in every sense of the word. I never have seen one who was more able to stimulate and encourage his patients and who failed less in doing so. Dr. Shattuck not only taught us to observe, but he taught us what no one else at that time was teaching in the Massachusetts General Hospital, and that was how to record our observations. He made exceedingly careful bedside notes. They were sometimes long for us to write as house officers, but they were exceedingly valuable when written down. He taught us something more, which was perhaps as valuable as anything else, and that was to love him.

Dr. Welch.—Just a word about Dr. Shattuck. His remarks bring back to me a good deal that used to be written in the Roman histories of my early days about succeeding consulships. That is a very good idea, and I do not know but that it might be adopted as a regular thing. A man retires from his consulship, is succeeded by somebody else and some five years later he makes a review which does not necessarily represent progress, but represents what changes resulted from a change in consulship. That is what interests me particularly about Dr. Shattuck's observations. I hope he will have the same opportunity to give us another five years' review. It would certainly be worth hearing.

Dr. Shattuck does represent, as Dr. Thayer has said, the very best type of doctor, combining the scientific and the practical, the interest in the case and the interest in the patient. No amount of scientific work will in itself alone make a great clinician. The great clinician must be a combination of that scientific interest and that practical quality, which can be acquired, although not always readily, which looks upon the patient not as material, not as a case, but as a human being.

DIABETES: THE RESULTS OF PAST TREATMENT AND FUTURE PROBLEMS[1]

By Elliott P. Joslin, M. D., Boston, Mass.

At the beginning of 1914, the outlook for diabetic patients was depressing. The statistics of the Massachusetts General Hospital showed that in the preceding 16 years for each 100 diabetics admitted 28 were discharged dead, a record which duplicated the experience of the hospital between 1824 and 1898. Physicians dreaded to place their patients in an institution lest the treatment there prescribed prove more disastrous than that adopted by the patient's fancy. Surgeons dodged the diabetic, while the obstetrician was out and out afraid of diabetes and urged pregnant women to have abortions. The neurologist, dermatologist and ophthalmologist would throw up their hands at complications within their respective spheres and exclaim, "Cure the diabetes and then we will help the patient." It is hard to realize that these conditions prevailed only four brief years ago.

As so often happens when the clouds are darkest, light unexpectedly appears, and I recognized its approach one afternoon while talking with Dr. Allen. It happened in this way: We were discussing one of my severest cases (Case No. 344) and I pointed out how the type of diabetes in this instance changed from severe to mild as tuberculosis came on and the patient progressively became weaker and lost weight. I remember telling Dr. Allen that if he could explain why this change took place the problem of diabetic treatment would be greatly advanced. The next day I heard from him that he felt he could explain the reason for the improvement, and furthermore believed that he would be able to demonstrate the cause for it by animals, and soon after I was gratified to learn how doctors could give their diabetic patients renewed hope. You are familiar with his experiments by which he showed that dogs made artificially diabetic and then forced progressively to lose weight gained in tolerance for carbohydrate.

The far-reaching results of these experiments immediately began to show, and are illustrated by the following table:

TABLE 1

The Recent Improvement in Diabetes as Shown by the Statistics of the Massachusetts General Hospital

Period	No. of cases	Mortality during hospital stay	
		No. of deaths	Per cent
1824-1898	172	47	27
1898-1914	284	80	28
1914	51	8	16
1915	89	11	12
1916	103	8	8
1917	105	6	6

[1] Presented before The Johns Hopkins Medical Society, February 4, 1918.

Your attention is directed to the stationary character of hospital diabetic mortality for 90 years and its abrupt and steady diminution following Dr. Allen's announcement. A reduction of mortality from 27 per cent to 6 per cent would appear to be sufficient proof of improvement, but other evidence is available. At the New England Deaconess and Corey Hill Hospitals there were under my care during 1917, 181 diabetic patients. Of these four died, a mortality of 2 per cent, and I believe that this year three of these patients could be saved. I have summarized my personal statistics in Table 2.

TABLE 2

Author's Statistics of Diabetic Patients Treated at the New England Deaconess and Corey Hill Hospitals

Year	No. of cases	Mortality during hospital stay	
		No. of deaths	Per cent
1913	43	4	9
1914	60	3	5
1915	109	6	6
1916	164	8	5
1917	181	4	2

What other disease, chronic or acute, can show a similar reduction in mortality during these last four years? After all, diabetes has points in its favor. Never forget that unlike cancer and rheumatism, it is painless; unlike tuberculosis, it is clean and not contagious, and in contrast to many diseases of the skin, it is not unsightly. Moreover, it is susceptible to treatment and the downward course of a patient can usually be promptly checked. It is true that treatment is by diet and not by drugs, but the patients who know the most, conditions being equal, can live the longest. There is no disease in which an understanding by the patient of the methods of treatment avails as much. Brains count, though knowledge alone will not save the diabetic. This is a disease which tests the character of the patient, and for successfully withstanding it, in addition to wisdom, it demands of the individual honesty, self-control and courage.

This striking improvement in diabetic treatment belongs to the first year of the disease, the year which I call the diabetic's danger zone. This is important, for it is the most useful year to the diabetic and to the community. The first year of the disease is pre-eminently the year of coma. Eighty-seven per cent of all diabetics who have come under my care and have later died during the first year of the disease have succumbed to it. And yet to-day everyone will agree that diabetic coma during the first year of the disease should be considered an accident which can and should be avoided not only in adults but in the youngest child.

How much the average length of life of the individual patient has been increased by our recent methods no one knows, but the following table gives my own personal experience, ending December 1, 1916. Eventually I hope to bring this table up to January 1, 1918, and to continue it still further. As it stands now the average length of life of my fatal cases for the different decades is considerably under the average length of life of the living cases. This is a hopeful sign.

TABLE 3[2]

Duration of Life of Fatal and Living Cases of Diabetes, December 1, 1916

Age at onset years	Fatal		Living	
	No. cases	Average duration	No. cases	Average duration
0–10	37	1.3	22	2.6
11–20	55	2.8	40	2.9
21–30	51	3.1	61	5.3
31–40	64	4.4	94	7.2
41–50	95	6.4	184	7.3
51–60	115	6.9	163	6.3
61–70	67	5.7	63	6.1
71–80	16	3.6	12	5.3
81–90	..	...	1	1.3

The prolongation of life holds quite as strongly with the young as with the old. It was rare formerly for a patient in the first decade of life to live more than a few months. Now the children are expected to live at least twice as long. This may not mean much in itself, but it does in the treatment of diabetes as a whole, and it demonstrates that if the duration of the disease in the severest cases has been doubled by the improved methods of treatment, marked gains in treatment ought to follow in the mild types. With the middle-aged I have been able to collect from my records 33 cases who have not only lived long, but have exceeded their theoretical expectation of life at the onset of their diabetes. Moreover, nearly a year ago Hornor and I[3] found that 5 per cent of the cases had lived over 15 years.

Mention was made of the surgeon's and obstetrician's avoidance of the diabetic patient in 1914. To-day I can testify from my own experience that without fear and with success surgeons remove the appendix, uterus, ovaries, prostate, gall-stones; resect cancers of the bladder or large areas of intestine on account of strangulation, and even operate on the lung. The obstetrician now carries his patients through labor without danger and there are a good many healthy children living to-day whose lives are a witness of improved diabetic methods. Neuritis and affections of the skin are rare exceptions. On January 26, 1918, Case No. 817, whose carbuncles were so extensive three years ago that the attending physician felt it was kindness to allow him to die, came into my office at the age of 76 years, having gained 59 pounds since I first saw him! I confess that it is not often that the diabetic of so many years' duration complains as did he of growing fat.

Improvement is also registered by successively severer and severer cases being rescued from coma. Six months ago I was able to publish a list of 15 severe cases of diabetes recovering from acidosis, with subsequent discharge from the hospital, without the use of alkalis.[4] Estimating the severity of these cases in terms of carbon dioxide tension of the alveolar air or of the blood, their acidosis was included between the boundaries of

[2] Joslin: Treatment of Diabetes Mellitus, 2d Edition, Lea & Febiger, Philadelphia, 1917.

[3] Am. Journ. Med. Sciences, 1918, Vol. CLV, p. 47.

[4] Joslin: *Loc. cit.*, Table 172, p. 389.

15 and 25 mm. mercury. Compiling a second series one month ago I was able to substitute seven cases in the original list by seven others still more severe, thus changing the limitations of the carbon dioxide to between 14 and 22. In anticipation of this meeting, I wrote Dr. Geyelin of New York and he has furnished me with cases of his own and at least three of these will replace three of mine, thus enabling a new series of 15 cases to be compiled of threatening coma treated successfully without alkalis, of which, thanks to Dr. Geyelin, the lowest limit, measured in terms of carbon dioxide tension, is reduced to 13.65 mm. mercury in the blood, and the highest limit to 20, measured in terms of carbon dioxide in the alveolar air. These results are shown in Tables 4 and 5.

TABLE 4

THREATENED DIABETIC COMA SUCCESSFULLY TREATED WITHOUT ALKALIS. THREE GROUPS OF CASES, 15 EACH, COMPILED AT SUCCESSIVE DATES, EACH GROUP SEVERER THAN THE PRECEDING.

Date of compilation	No. cases	Limits of degrees of acidosis CO_2 in terms of mm. Hg. in blood or alveolar air
September, 1917	15	15–25
January, 1918	15	14–22
February, 1918	15	13.7–21

TABLE 5

SUCCESSFUL TREATMENT WITHOUT ALKALIS OF 15 CASES OF DIABETES THREATENED WITH COMA

Case No.	Date	FeCl.	NH_3 grams	Blood CO_2 mm. Hg.	Alveolar air CO_2 mm. Hg.
691	Nov. 15, 1917...	+	...	..	20
1200	May 29, 1917 ...	+++	2.3	..	18
786	June 11, 1916...	++	3.9	..	18/20
	12	+	3.2	24	21
Dr. Geyelin J. G.	May 31, 1917...	+++++	...	13.7	..
942	July 12, 1916...	+++	4.4	20	20
	13	++	3.7	..	17
938	Nov. 2, 1917....	++++	1.3		18
Dr. Geyelin M. S.	Apr. 5, 1917.....	+++++	...	21	..
Dr. Geyelin H. J.	Oct. 18, 1917...	+++++	...	16	..
755	Apr. 15, 1917...	+	1.6	..	18
1011	Mar. 29, 1916...	++	1.8	..	23
	Apr. 13, 1916...	++	...	..	22
	Sept. 25, 1917...	++++	...	..	15
1085	Oct. 30, 1916....	?	1.7	28	20
1196	Dec. 8, 1916	++++	4.6	..	21
	9	++	6.0	26	22/14
	10	+++	3.3	..	18/20
	11	+	3.1	26	20
	12	++	3.3	..	21
	13	++	2.9	..	24
1070	June 23, 1916...	++	1.9	21	20
1012	Sept. 13, 1917 ..	+++	...	..	14
	14	+++	2.5	21.3	14
	15	?	2.3	..	16
1120	Sept. 6, 1916 ...	+++	...	..	21
	7	+	...	..	18
	Oct. 11, 1916 ...	++	1.9	..	22
	14	0	...	..	20
	27	+	...	..	15

Individual cases are more striking than convincing. Each month I derive encouragement from the return of an old case. A recent one is Case No. 866, first seen in 1915 at the age of 32 with onset one year before, whose consumption of food prior to admission to the hospital in 1915 was extraordinary even for a diabetic. His regular ration was two dozen eggs, three pounds of meat and 30 apples, with other food unrecorded. The sugar in the urine at this time amounted to 4 per cent. On January 28, 1918, he again returned to the hospital, after an absence of three years, but this time sugar and acid free and with the report of having remained so almost constantly! During the interval he had at no time gone to a physician's office and at no time missed work on account of illness. His present diet and method of living interested me extremely, for it shows what a courageous man can do. It consists of a pound of cabbage at each meal, and for the day two eggs, 60 grams of bacon (weight uncooked), six ounces of meat at dinner and the same for supper, 120 c. c. of 20 per cent cream, and about 60 grams of butter. I do not report this as an ideal diet, but upon it this man has supported his family and lost but six and one-half pounds in weight in three years. Mark this! He retires at 8 p. m. and rises at 6 a. m., 10 hours in bed! The course of this case should be compared with the course of patients who suffer from other chronic diseases. How many nephritic, cardiac, arteriosclerotic or chronic rheumatic patients could touch as low a limit of life as this patient three years ago and regain to such an extent their efficiency?

I do not share the opinion of some hospital clinicians who in the face of cases like this, and in these days when the hospital diabetic mortality has been lowered from 28 to 2 per cent, pretend to be discouraged about the treatment of diabetes and are prone to fill their wards with patients showing interesting electrocardiagrams whose efficiency can seldom be regained.

Will the recent improvement in treatment continue? I believe it will, and for three reasons. First of all, the trend of statistics points to it, as is proven by a study of the statistics of the Massachusetts General Hospital. You have undoubtedly observed that the reduction in hospital mortality has taken place gradually. Each year has shown progress, and my own figures illustrate that this improvement can proceed still further. In the second place, the enemies of the diabetic are now more clearly recognized. We know exactly with what we must contend. This is evident from Table 6.

TABLE 6

CAUSES OF DEATH OF 516 DIABETIC PATIENTS SEEN IN PRIVATE PRACTICE ONE OR MORE TIMES FROM 1894 TO DEC. 11, 1916

Coma	60	per cent
Cardiorenal	13	" "
Infections	10	" "
Cancer	5	" "
Tuberculosis	4	" "
Inanition	1	" "
Miscellaneous	6	" "

I would particularly direct your attention to the 60 per cent of deaths due to coma and the 1 per cent of deaths due to inani-

tion. Since fasting treatment, introduced by Dr. Allen, has been adopted, the fear has arisen that inanition would figure prominently as a cause of death of diabetic patients. As yet this has not proven to be the case. Inanition will undoubtedly increase in frequency, but I shall not allow it to divert my attention from the 60 per cent of the cases who die of coma. All but two of my fatal cases in children have died of coma. Of all the diabetics coming under my supervision, 87 per cent of those who have died during the first year of the disease have succumbed to coma, and even 44 per cent as well of those cases who have lived more than 15 years. The one enemy which the diabetic must fight is coma. Thirteen per cent of the patients died of cardiorenal disease, but with modern treatment adapted to impaired kidneys the lives of such patients might be easily prolonged. Infections continue to be a great menace, but are not nearly so serious as formerly, when they were so often complicated by coma. We must expect that the mortality from cancer will rise, and can look for a continued lowering in the mortality from tuberculosis due to the lessened opportunities for contagion. It is better avoided than treated, but even if present does not preclude many years of life.

The third reason for the continued improvement in the treatment lies along several lines. (A) Earlier diagnoses of the disease are being made. By this means, mild cases are discovered and their change into a severer type is delayed or prevented. (B) Coma can be avoided to-day in the overwhelming majority of cases. Whereas formerly numberless diabetics died at the beginning of treatment, to-day such a death excites comment in any well-regulated hospital. Attention has been called to the decrease in coma after surgical operations due to the measures adopted to prevent acid-poisoning and the decreased use of ether as an anesthetic. (C) A new type of ammunition in the battle against diabetes is now being generally adopted. I refer to the education of the doctor, nurse and, most of all, the patient. Whether teacher and student desire to devote increasing time to the study of diabetes, the fact remains that there are four times the number of cases in the United States recognized to-day as in 1890, and thus four times as many to be treated. Instruction in diabetes, therefore, should receive four times the time allotted to it in the curriculum. Diabetes is pre-eminently a disease in which education avails. Fortunately, with the treatment introduced by Dr. Allen, the education both for doctor and patient has been so simplified that the essential facts can be summarized on a small card.

The training of the patient in hygiene, diet and clinical tests constitutes a new era in medicine. Previously tuberculosis was the disease where the education of the patient was most insisted upon and in that hygiene alone was the only subject taught. Many advantages will accrue from the war and not the least of these is the compulsory education of patients and of nurses in matters hitherto supposed to be beyond their ken. To-day I know a group of nurses who specialize in diabetes, and I can trust any one of these nurses to go into a patient's home and carry out treatment from beginning to end, simply depending upon the family physician for general supervision.

The Treatment of Diabetes as Practiced To-day.—The treatment of diabetes as it is actually practiced to-day is very different from what it should be. By no means does it follow the lines advocated at the Rockefeller Institute, The Johns Hopkins Hospital or other large hospitals in the country. I honestly believe that more cases of diabetes are now treated with the diet which appears on the back of a drug firm's advertisement than by any other method. It is still a rarity for a patient to come to me free from sugar and free from acidosis, and the cases are few and far between who have any conception of dietetic values. Diagnoses of diabetes are still made too late. Unfortunate as this is, I am glad to say that I have noted definite signs of improvement, chiefly manifested in the lessened use of drugs. The general practitioner is not to be too sharply criticized, because the methods which are employed in the leading institutions are only of recent origin, and furthermore, the general practitioner has never had a consistent plan for the treatment of diabetes laid out for him. It would be a great mistake if our present simple methods were to be rapidly changed purely for the sake of some slight improvement. When we realize the great advance in the treatment of diabetes which has taken place during the last four years, and at the same time bear in mind the intricate but definite problems which lie ahead, and appreciate the difficulty of interpreting the mass of scientific data just accumulated, we should hesitate long before altering the methods which have brought these gains. In the past, waves of diabetic treatment have followed in rapid succession. From nearly each one of these something has been gained. Let us be sure that we gather the benefit of all the good which is coming in on the present crest before we dive into a new breaker.

What Should be the Treatment of To-Day?—In general, authorities agree. The patient should be made sugar-free and this should be done in such a manner as not to produce acid intoxication. The basic principle is fasting, and it makes little difference whether the fasting is absolute or partial. Some of us prefer to omit the fat in the diet before the fast in the hope of warding off acid poisoning, which occurs in a small number of cases following the fast. This method has been most satisfactory in my hands. By this means, along with the prevention of acid poisoning, the patient gets the benefit, without the hardships, of reduced calories. The rules which I follow in the treatment of my cases are very simple, and although I seldom follow these to the letter, for each case is unto itself, I have found the method of treatment so satisfactory that I shall perhaps be more loath to change it than those of you who are just starting in medicine and have not lived through the barren years of diabetic treatment. These schematic rules and the dietetic values necessary for the patient are recorded on this small card, the reading of which may be omitted.

Preparation for Fasting. In severe, long-standing, complicated, obese, and elderly cases, as well as in all cases with acidosis, or in any case if desired, without otherwise changing habits or diet, omit fat, after two days omit protein, and then halve the carbohydrates daily until the patient is taking only 10 grams; then fast. In other cases begin fasting at once.

Fasting. Fast four days, unless earlier sugar-free. Allow water freely, tea, coffee, and thin, clear meat broths as desired.

Intermittent Fasting. If glycosuria persists at the end of four days, give 1 gram protein or 0.5 gram carbohydrate per kilogram body weight for two days, and then fast again for three days unless earlier sugar-free. If glycosuria remains, repeat and then fast for one or two days as necessary. If there is still sugar, give protein as before for four days, then fast one, and then gradually increase the periods of feeding, one day each time, until fasting one day each week. I have seen no uncomplicated case fail to get sugar-free by this method.

Carbohydrate Tolerance. When the twenty-four-hour urine is free from sugar give 5 or 10 grams carbohydrate (150 to 300 grams of 5 per cent vegetables) and continue to add 5 or 10 grams carbohydrate daily up to 50 grams or more until sugar appears.

Protein Tolerance. When the urine has been sugar-free for three days, add about 20 grams protein and thereafter 15 grams protein daily in the form of egg-white, fish or lean meat (chicken) until the patient is receiving 1 gram protein per kilogram body weight or less if the carbohydrate tolerance is zero.

Fat Tolerance. Add no fat until the protein reaches 1 gram per kilogram body weight (unless the protein tolerance is below this figure) and the carbohydrate tolerance has been determined, but then add 5 to 25 grams daily according to previous acidosis until the patient ceases to lose weight or receives in the total diet about 30 calories per kilogram body weight.

Reappearance of Sugar. The return of sugar demands fasting for twenty-four hours, or until sugar-free. Resume the former diet gradually adding fat last in order to maintain as high a carbohydrate tolerance as possible, sacrificing body weight for this purpose.

Weekly Fast Days. Whenever the tolerance is less than 20 grams carbohydrate, fasting should be practiced one day in seven; when the tolerance is over 20 grams carbohydrate cut the diet in half on one day each week. The foods commonly employed in determining the tolerance for carbohydrate and protein are 5 per cent vegetables, oranges, oatmeal, potato, fish, chicken, lean meat.

1 gram protein,	4	calories.	1kilogram = 2.2 pounds.
1 " carbohydrate,	4	"	30 grams (g) or cubic centimeters (c. c.) = 1 ounce.
1 " fat,	9	"	A patient at rest requires 25 calories per kilogram body weight; approximately 1 calorie per kilo. per hour.
1 " alcohol,	7	"	
6.25 " protein contain	1g.	nitrogen.	

Consult Chemical Composition American Food Materials, Bull. 28, U. S. Dept. Agriculture, by sending 10 cents in coin to Supt. of Documents, Washington, D. C., also Annual Report Conn. Agricultural Experiment Station, New Haven, Conn., Food Products and Drugs, 1913, Part 1, Section 1.—Free.

Water, clear broths, coffee, tea, cocoa shells and cracked cocoa can be taken without allowance for food content.

FOODS ARRANGED APPROXIMATELY ACCORDING TO CONTENT OF CARBOHYDRATES

	5% *	10% *	15%	20%
VEGETABLES (fresh or canned)	Lettuce, Cucumbers, Spinach, Asparagus, Rhubarb, Endive, Marrow, Sorrel, Sauerkraut, Beet Greens, Dandelion Greens, Swiss Chard, Celery, Tomatoes, Brussels Sprouts, Water Cress, Sea Kale, Okra, Cauliflower, Egg Plant, Cabbage, Radishes, Leeks, String Beans, Broccoli	Pumpkin, Turnip, Kohl-Rabi, Squash, Beets, Carrots, Onions, Mushrooms	Green Peas, Artichokes, Parsnips, Canned Lima Beans	Potatoes, Shell Beans, Baked Beans, Green Corn, Boiled Rice, Boiled Macaroni
FRUITS	Ripe Olives (20% fat), Grape Fruit, Lemons.	Oranges, Cranberries, Strawberries, Blackberries, Gooseberries, Peaches, Pineapple, Watermelon	Apples, Pears, Apricots, Blueberries, Cherries, Currants, Raspberries, Huckleberries	Plums, Bananas, Prunes
Nuts	Butternuts, Pignolias	Brazil Nuts, Bk. Walnuts, Hickory, Pecans, Filberts	Almonds, Wal'ts (Eng.), Beechnuts, Pistachios, Pine Nuts	Peanuts
Misc.	Unsweetened and Unspiced Pickle, Clams, Oysters, Scallops, Liver, Fish Roe			40% Chestnuts

* Reckon carb. in veg. of 5% group as 3%—of 10% group as 6%.

(30 grams 1 oz.) CONTAINED APPROXIMATELY	CARBOHYDRATES G	PROTEIN G	FAT G	CALORIES
Oatmeal, dry wgt.	20	5	2	120
Cream, 40%	1	1	12	120
" 20%	1	1	6	60
Milk	1.5	1	1	20
Brazil Nuts	2	5	20	210
Oysters, six	4	6	1	50
Meat (uncooked, lean)	0	6	3	50
" (cooked, lean)	0	8	5	75
Bacon	0	5	15	155
Cheese	0	8	11	135
Egg (one)	0	6	6	75
Vegetables 5% group	1	0.5	0	6
Vegetables 10% group	2	0.5	0	10
Potato	6	1	0	30
Bread	18	3	0	90
Butter	0	0	25	225
Oil	0	0	30	270
Fish, cod, haddock (cooked)	0	6	0	25
Broth	0	0.7	0	3
Small orange or ½ grape fruit	10	0	0	40

Form J 8. Thomas Groom & Co., Inc., 105 State St., Boston

Throughout the course of treatment the education of the patient in the hygiene of his life, in his diet and in the examination of his urine should be promoted. Like others, I have devised various forms of printed matter, and in fact have just completed for patients a sort of diabetic primer[5] which I hope they will actually study. This is designed not only to educate the patient, but to save the physician's time.

Acidosis should be prevented by the rules of diet prescribed by the doctor and adopted by the patient. In general, given a patient without acidosis, one can avoid its onset. The elimination of fat at the beginning of treatment and its elimination later whenever signs of acid poisoning appear is a safe rule. I have not used alkalis for some years. Until a group of cases, more severe than the 15 already cited, is reported to have recovered by some other method, I recommend to your consideration the plan of treatment which has yielded these results.

THE TREATMENT OF THREATENING DIABETIC COMA

The following rules are in force at the New England Deaconess and Corey Hill Hospitals:

1. *Nursing.*—Provide a special nurse for the patient both day and night, and, preferably, one trained in diabetic work.

2. *Bed.*—Keep the patient in bed and warm. Avoid loss of calories through exertion or exposure; if restless, protect from becoming chilled by flannel night-clothes. Every effort should be made to allay nervousness and discomfort.

3. *Bowels.*—Move the bowels by one or more enemata. Cathartics should usually be avoided for fear of causing diarrhea.

4. *Stomach.*—The stomach should be free from indigestible food. With adults, when in doubt, but with children in all cases, begin treatment with gastric lavage.

5. *Heart.*—Sustain the circulation with the help of digitalis. Caffein may be given subcutaneously, or as black coffee by rectum.

6. *Administration of Liquids.*—Give 1000 c. c. of liquids within each six hours. The liquids are to be given slowly, hot, as coffee, tea, thin broths, water; if the prospect is dubious of giving so much liquid by mouth, salt solution or tap-water is to be given by rectum; if this resource fails, the nurse should call the doctor to give intravenously the balance of the liter which remains not given for the period. (It will seldom be found necessary to give more than 1000 c. c. liquids, thanks to the avoidance of alkalis.) In order to secure the introduction of sufficient liquid in the first six hours the cleansing enema at the beginning of treatment should be followed after half an hour by an enema of 500 c. c. salt solution in all cases as a matter of precaution.

7. *Diet.*—If the patient has been accustomed to the fasting method of treatment, begin or continue the fast, but if he has been upon a full diet, give 1 gram of carbohydrate per kilogram body weight during the 24 hours in the form of orange

[5] **A Manual of Diabetic Treatment for Doctor and Patient. Lea & Febiger. Philadelphia, 1918.**

juice or gruel (oatmeal) made with water; or as many grams of carbohydrate as the patient has voided in the urine in each successive preceding six hours. Whichever course is adopted, it is to be followed until danger is over.

8. *Alkalis.*—Avoid alkalis. If such have been previously given, omit at the rate of 30 grams a day.

Many diabetic problems demand solution to-day, and it is encouraging that they stand out in relief far more distinctly than ever before. Many of these problems do not require great discoveries for their elucidation, but simply plain hard work. Thanks to Dr. Allen, it is fortunate that so many of these can be worked out upon animals. By this means results can be more quickly secured.

1. The one question which I hope most to see solved within the next two years, is whether the tolerance of a mild diabetic for carbohydrate is lowered by our present methods of treatment in making him sugar-free. Perhaps Dr. Allen has already settled this point. Clinically, every once in a while one sees a patient with a high tolerance who loses the tolerance in a comparatively short course of time, although the best modern methods are followed. Thus Case No. 914, with a tolerance for 140 grams carbohydrate a year and a half ago, has now a tolerance for but 10 grams. This is so different from what I expected to occur in this case that I can hardly believe it necessary, and wonder whether some error in treatment has not been made. Of course it is possible that a year and a half ago by our former methods the tolerance would not have appeared nearly as high, and that at the start the case was really far more severe than was considered. I am sure that many of you have had similar experiences. We should not allow these apparently mild cases to change to severe without the sharpest possible fight. This question is of the utmost importance. Take, for example, two children in one family living not far from this city, who have apparently very, very mild diabetes. Should they be kept absolutely sugar-free or upon a restricted diet, but not a diet of undernutrition? This is the sort of a problem for the solution of which your wealthy diabetic should give your hospital $50,000. It demands both clinical and experimental work, and it is justifiable to hold out the hope of securing useful results.

2. The next problem to interest me is whether the tolerance of the diabetic can be raised. Already considerable data have been accumulated at the Nutrition Laboratory of the Carnegie Institution by Benedict and myself, and eventually this will be published. In it are hints of such a possibility. The spectacular absence of sugar in the urine following the administration to the severe fasting diabetic of large quantities of levulose and of some other carbohydrates is encouraging. How these patients can bear so much carbohydrate at one time when at another a few leaves of lettuce cause glycosuria is hard to understand. The fact that repeatedly the respiratory quotient rises in such individuals is of significance, just as is the high respiratory quotient of severe diabetics during fasting.

3. The increased lipoid content of the blood and the measures necessary to reduce it is a third problem. The 400 analyses of blood lipoids made by Gray upon my patients have interested me greatly, and have shown the need for more. From them I am beginning to learn a few suggestions as to how the fat can be reduced. But when I heard the other day that in addition to the numerous analyses made under Dr. Allen's direction upon the blood lipoids of his patients there still remained 5000 more specimens to analyze, I could not help feeling that perhaps we were nearer to the discovery of the method by which the high blood fat could be reduced than we supposed.

4. The high blood sugar and its reduction in diabetes is a tempting target. Is this really worth while? I think it is, but I would be glad to have more evidence. When I see a patient who has outlived the average period of life of my living cases for the corresponding decade of age, who appears in good condition, as does Case No. 600, and yet shows a blood sugar of 0.21 per cent, but is sugar-free, I hesitate to change the method of treatment which has worked so well so many years. Time perhaps will settle this question for us, for who knows how long this patient has had so high a blood sugar? During the first five or six years of her treatment, no blood sugar test was made. To me it appears that she will live for many years to come, and although she may not reach her expectancy of life, which would mean a duration of the diabetes of 21 years in her special case, yet there appears to be a fair chance of her doing so. Would this patient really be benefited, now that she is sugar and acid free, by having her blood sugar brought to normal? I never see her without thinking, "Fools step in where angels fear to tread," and at present I want to be numbered with the angels.

5. Edema and even anasarca in the severe diabetic are symptoms often accompanied by well being on the patient's part. Why do some diabetics feel so much better when they have dropsy than when the water content in their tissues is normal or even below normal? At present I can remember but one of my diabetic patients who has shown marked dropsy who has not been freed of it by simple restriction of salt. Just recently I have reported[*] one case, Case No. 1012, where a gain of 25 per cent weight in the form of edema was present, and another patient now under my care has lost an equal amount. If patients do not go into coma when they have dropsy, why not make them have dropsy when coma is threatening? Dr. Hornor and I have partially attempted this in one case, but I would like to have it literally carried out and see the patient's weight increase not one or two pounds in the course of a day, but by 10 to 20 per cent. It would not do to inject so much fluid directly into the circulation because of the failing heart, but the fluid could be introduced under the skin or into the abdominal cavity.

These are only a few of the diabetic problems which you have to solve. Most of them appear capable of solution. They will not be settled except by aid from many workers, and in their solution not alone should the help of doctors and medical students be utilized, but that of technicians to the widest possible degree. While absorbed in our endeavors let us not forget that when a diabetic life is prolonged for even a day, fresh hopes for millions of diabetics throughout the world are created.

[*] Med. Clin. of North America, January, 1918.

A STUDY OF AN AUTOAGGLUTININ OCCURRING IN A HUMAN SERUM

By MILDRED C. CLOUGH, M. D., and INA M. RICHTER, M. D.

(From the Medical Clinic of The Johns Hopkins Hospital)

Autoagglutination, that is, agglutination of red blood corpuscles in the presence of serum from the same individual, is an extremely uncommon occurrence in human beings. Indeed, some authors (1, 2, 3) state that this never occurs. The following instance is reported on account of certain interesting observations brought out in a study of the autoagglutinin, as well as on account of the rarity of the condition. This phenomenon was first noticed in our case on making a routine red blood cell count. It was found upon drawing the blood into the diluting pipette that the red blood cells became agglutinated so markedly that clumps were visible macroscopically as well as microscopically. The agglutinated cells could not be broken up upon shaking, and an accurate count of them was impossible.

The literature on the subject of autoagglutination is very meager. The first reference to this phenomenon is by Reitmann (4) in 1890. He noted, on making a red blood cell count in a case of cirrhosis of the liver, that "the red blood-corpuscles were strikingly sticky, three or four sticking together." No further observations on the blood are recorded, but it seems likely that this occurrence was due to autoagglutination. Ascoli (5) in 1901, stated that, in a study of the blood of 17 normal individuals, he found in a number of instances that the serum was able to agglutinate the red blood corpuscles of the same individual, as well as those of other individuals. This report, however, is open to question. It seems very improbable that this rare phenomenon should occur a number of times among only 17 specimens of blood examined. This surprising statement is probably to be explained by the fact that he apparently regarded rouleaux formation as a form of agglutination. Klein (6) in 1902, noticed autoagglutination in the blood of a horse and stated in this report that in 1890, in a case of hypertrophic liver cirrhosis, he was unable to make a red blood cell count, because the cells, when drawn into the diluting fluid, stuck together in masses in which the cell boundaries could scarcely be made out. He considered it a phenomenon peculiar to liver cirrhosis, and said that Obermayer in Nothnagel's clinic stated in a personal communication that he had confirmed Klein's observation in a series of cases of hypertrophic liver cirrhosis. Landsteiner (7) in 1903, again noted autoagglutination in the blood of horses and other animals. He found that the agglutinin was fixed to the cells at low temperatures, and if the washed, agglutinated red blood corpuscles were suspended in warm salt solution the clumps broke up, and agglutinin could be demonstrated in the salt solution. He considered that cold exerts a favoring influence on isoagglutination also, and that isoagglutinins can be partially liberated by warming (8). He isolated the auto- as well as the heteroagglutinins in the globulin fraction of the serum (7). Hektoen (9) in 1906, stated that he observed autoagglutination and autophagocytosis in the blood of two individuals, but in a later article (10) said that "autoagglutinins are very seldom, if ever, demonstrable in vitro." Rous (11) has produced autoagglutination in the blood of rabbits, and Ottenberg and Thalhimer (12) report its occurrence in cat's blood.

The following is a brief abstract of the history of the patient in whose blood autoagglutination was observed:

CASE HISTORY.—Med. No. 38768. L. T.; 32 years; female. Russian Jew. Married. Adm. Oct. 19, 1917. Discharged Nov. 28, 1917. Family and past history negative. One week before admission the patient "caught cold," with fever, cough, dyspnea, palpitation, and pain in the right side of the chest. Physical examination on admission showed signs of a diffuse bronchopneumonia, and of mitral stenosis and insufficiency with auricular fibrillation. These findings were confirmed by X-ray and electrocardiographic examinations. Sputum culture showed both B. influenzæ and Staphylococcus aureus. Blood culture and Wassermann reaction were negative. Urine normal, except for a trace of albumin, and, for a few days after admission, a trace of urobilin. The pulse ranged from 65 to 110; blood pressure from 100/50 to 120/70. The temperature ranged from 100°-104°, gradually falling to normal four weeks after admission. The blood findings on admission were: red blood cells, 4,736,000; white blood cells, 9600; hemoglobin 100 per cent. During the fever there was a polymorphonuclear leucocytosis of from 10,000 to 24,000. The hemoglobin fell to 70 per cent and the red cells to 4,000,000 at the height of the infection, but rose to 90 per cent and 4,900,000 on discharge. Except for the count made on admission, it was impossible to make a red blood cell count during the febrile period on account of the autoagglutination, unless the solution were warmed. With recovery and return to normal temperature, warming above ordinary room temperature was no longer necessary. The agglutinating activity of the serum then seemed to be somewhat feebler, and to require a lower temperature for its manifestation. We do not, however, attach very great significance to this observation for reasons which will be discussed later.

The phenomenon of autoagglutination was first noticed in our case on diluting the blood for a red cell count. New pipettes and new diluting fluids were used for a second count to eliminate the possibility that the agglutination was caused by dirty apparatus or improperly prepared solutions, but agglutination again occurred. It seemed obvious, then, that the peculiarity was inherent in the blood itself.

In order to study this phenomenon, it was necessary to obtain serum, and unagglutinated red blood corpuscles free from serum. It occurred to us that agglutination might be prevented if the blood were kept warm, and the red cells washed several times in warm salt solution. It seemed inconceivable that the red blood cells were agglutinated in the circulating blood, and this suggested that the phenomenon might have been initiated at least by a lowering of the temperature of the blood. Also, by analogy with the hemolysin of paroxysmal

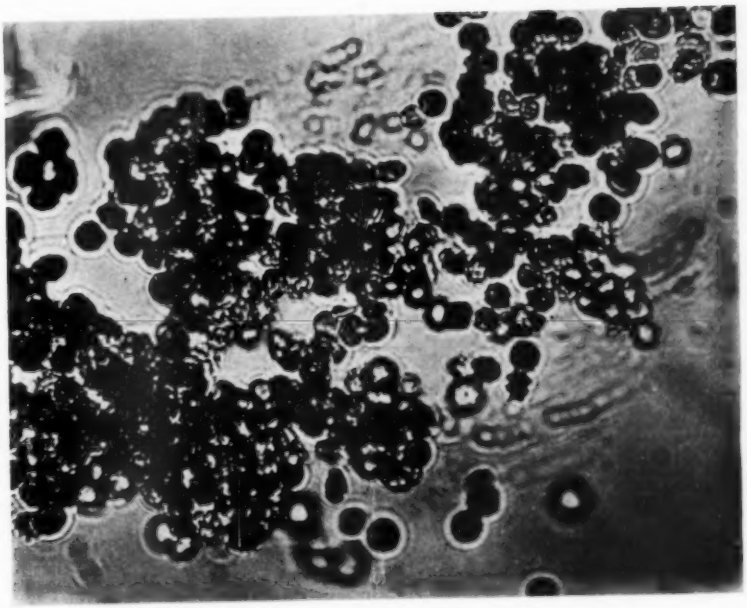

FIG. 1.

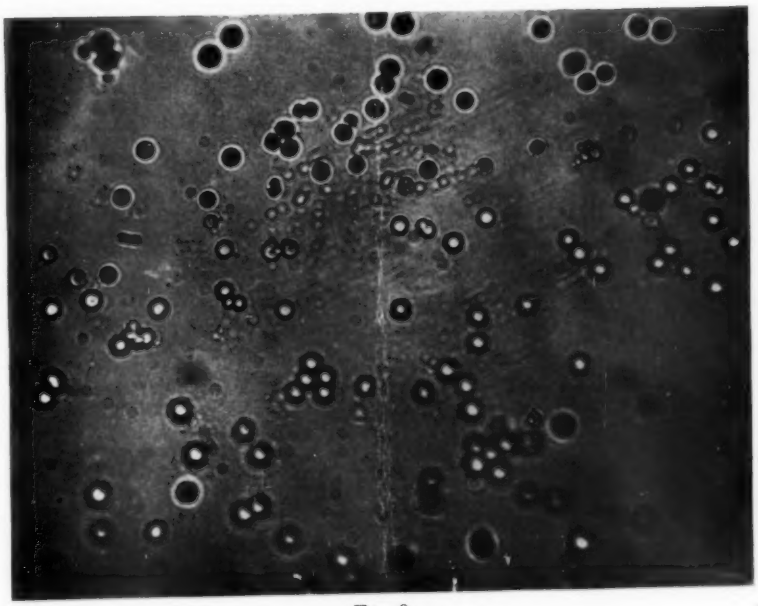

FIG. 2.

hemoglobinuria, which is fixed only at low temperatures, it seemed possible that fixation of the agglutinin might be avoided by washing the blood at body temperature. The observations of Landsteiner (7, 8) on the favoring effect of cold upon iso- and autoagglutination also suggested this method of obtaining unagglutinated red blood cells free from serum.

Accordingly, 10 c. c. of blood were obtained by venapuncture with a warm syringe. Five cubic centimeters of blood were allowed to clot in a test-tube to obtain serum, and the remaining 5 c. c. were added to 100 c. c. of sodium citrate solution warmed to 37° C. This mixture was immediately centrifugalized, and the cells washed twice in warm salt solution, great care being taken to keep the temperature constantly at or near 37° C. No agglutination of the red blood cells occurred during the washing.

A small amount of the original blood citrate mixture was kept separate, and allowed to stand at room temperature. In a few minutes marked agglutination became apparent macroscopically and microscopically. After placing the mixture in the thermostat at 37° for a short time, the agglutinated clumps of red blood cells broke up. In a hanging drop preparation the individual cells were seen to be perfectly preserved and evenly distributed throughout the suspension. This mixture was now placed in the ice-chest for a few minutes, and agglutination reappeared, and again disappeared entirely after warming to body temperature. This procedure was repeated several times with the same result.

A one per cent suspension of the washed red blood cells was then made in salt solution. Chilling this suspension caused no agglutination. The addition of a little of the patient's serum to part of the suspension, however, caused marked agglutination of the patient's red blood cells when the preparation was chilled. This agglutination, likewise, disappeared on warming to 37° C.

From these experiments it seemed probable that the peculiarity of this blood was present in the serum and not in the red blood cells. In order to study the action of this serum on red blood cells from other individuals, and of other sera on the red cells of this individual, the group of the patient was determined by the method suggested by Moss (13). Microscopic preparations were made of the patient's serum with red blood cells from individuals of groups 2 and 3, and also of the patient's red cells with serum of groups 2 and 3. The following results were obtained:

1. Group 2 serum + patient's red blood cells. Room temperature. One hour. Agglutination. This was not increased by chilling the mixture, nor were the clumps broken up by incubation at 37° C.

2. Group 3 serum + patient's red blood cells. Room temperature. One hour. No agglutination either at room temperature or in the ice chest.

3. Patient's serum + group 2 red blood cells. Room temperature. One hour. Agglutination similar to that in preparation 1.

4. Patient's serum + group 3 red blood cells. Room temperature. One hour. Slight agglutination at room temperature, which became marked on chilling in the ice-chest, and which completely disappeared on warming to 37°.

One could conclude, therefore, from these tests that the patient belonged to group 3. The agglutination occurring in preparation 4 differed from ordinary isoagglutination in its disappearance at 37°, and was evidently identical with that caused by the action of the patient's serum on her own red cells. In order to test this further, another preparation was set up with group 4 red blood cells.

5. Patient's serum + group 4 red blood cells. Room temperature. One hour. Agglutination similar to that in test 4, disappearing completely on warming.

It follows from these tests that there is no peculiarity in the patient's red blood cells to account for the autoagglutination. The patient's red blood cells were not agglutinated by the serum of another individual belonging to group 3, while the red blood cells of other individuals of groups 3 and 4 were also agglutinated in this peculiar way by the patient's serum.

This serum, then, has two distinct types of agglutinating activity on human red blood cells, (1) the usual isoagglutinating activity manifested by sera from all individuals belonging to group 3 for cells from individuals of groups 1 and 2, (2) an agglutinating activity, manifested only at low temperatures for cells of the patient herself, and for cells of all individuals tested regardless of the blood group to which they belonged.

The substance causing the second type of agglutination must, therefore, be regarded as both an autoagglutinin and an isoagglutinin. Furthermore, as will be shown later, this substance has the power of agglutinating the red blood cells of various species of animals, and must, therefore, be a heteroagglutinin as well. However, we shall follow the custom of using the term autoagglutination for this phenomenon to distinguish it from ordinary isoagglutination and heteroagglutination, bearing in mind, however, that it does not fully define the agglutinating activity of the serum. A more accurate term would perhaps be "cold agglutination."

Fig. 1 shows the autoagglutination of the patient's cells by her own serum at room temperature. Fig. 2 shows the same preparation after warming. The clumps are nearly, but not entirely, broken up. Further warming would have resulted in complete separation of the cells. In preparations showing marked agglutination, the macroscopic and microscopic appearances are identical with those of cells agglutinated by an ordinary agglutinating serum. When the reaction is less marked, as in high dilutions of serum, or at temperatures only slightly reduced, the clumps are looser and the individual cells less distorted. In preparations showing minimal degrees of agglutination, the cells are simply assembled in small clusters, without heaping up of the cells or deforming of their outlines. No rouleaux formation was observed in the preparations.

The properties of the patient's serum were then studied in the following ways:

Progressively increasing dilutions of the serum were made (from 1-2 up to 1-4000). To 0.25 c. c. of each dilution was added an equal volume of a 1 per cent suspension of the

patient's red blood cells and the mixtures placed in the ice-chest. At the end of 30 minutes agglutination was evident macroscopically in all dilutions of the serum up to and including 1-250, and after 24 hours also in 1-500. (These figures represent the final dilutions of the serum after the addition of the red blood cell suspension). This agglutinating substance, then, was present in the serum in high concentration.

In order to determine the highest temperature at which agglutination was initiated, a similar series of tubes was set up. These tubes were then cooled by immersion in a water bath, the temperature of which was gradually reduced. Agglutination was determined macroscopically. The results are shown in the following protocol:

30°	Half hour.	No agglutination.
27°	"	"
24°	"	"
22°	"	Agglutination in dilutions of serum up to 1–4.
19½°	"	" " " " " " " 1–8.
17°	"	" " " " " " " 1–30.
15°	"	" " " " " " " 1–30.
12°	"	" " " " " " " 1–250.
Ice chest over night.		" " " " " " " 1–500.

A similar experiment with dilutions of serum to which were added red blood cells of an individual belonging to group 4 gave identical results, indicating that the patient's cells were neither more nor less resistant to the agglutinating activity of her serum than were normal cells. Both sets when maintained at 22° for three hours showed agglutination in dilutions of serum up to 1-60. The critical temperature, therefore, appeared to be about 22° C.

The above set of tubes was then warmed gradually to see at what temperature the agglutination would disappear. The following results were obtained:

25°	Half hour.	Agglutination	unchanged.
30°	"	"	"
34°	"	"	partially broken up.
34°	One hour.	"	completely broken up.

This experiment indicated that agglutination persisted at a temperature higher than that necessary for its initiation.

In order to determine the nature of this autoagglutinating substance in the serum, further tests were carried out.

1. Heating the serum in 1-5 dilution at 60° for 1/2 hour did not diminish its activity, while heating to 65° for 1/2 hour destroyed entirely its ability to cause agglutination of the patient's red blood cells.

2. Dialyzing the serum in collodion sacs against physiological salt solution for 24 hours did not impair its agglutinating ability.

3. Extraction of the serum with chloroform did not remove these agglutinins.

4. Precipitation of the globulins from the serum by ammonium sulphate resulted in disappearance of the agglutinin from the serum. First the "euglobulin" was precipitated by the addition of 36 volumes per cent of a saturated solution of ammonium sulphate. The precipitate was washed in 36 per cent saturated solution of ammonium sulphate, and dissolved in physiological salt solution. The ammonium sulphate was then removed by dialysis. This euglobulin solution caused marked agglutination of the patient's washed red blood cells in the cold, like that produced by untreated serum. The "pseudoglobulin" was next precipitated from the serum by the addition of saturated ammonium sulphate solution to a concentration of 44 volumes per cent. The precipitate was then washed with 44 per cent saturated solution of ammonium sulphate, filtered, dissolved in physiological salt solution, and dialyzed. This pseudoglobulin solution caused no agglutination of the patient's red blood cells. The serum from which euglobulin and pseudoglobulin had been precipitated was dialyzed to remove the ammonium sulphate, and tested with the patient's red blood cells. No agglutination occurred. It was clear, then, that this autoagglutinin was associated with the "euglobulin" of the serum, as has been demonstrated in connection with iso- and other agglutinins.

Further work on the nature of the agglutinin was done in connection with absorption experiments, and will be discussed with them in a later paragraph.

The serum of the patient was tested for the presence of an autohemolysin analogous to that occurring in the serum of patients with paroxysmal hemoglobinuria. As shown by Donath and Landsteiner (14) and others, the serum from these patients contains an autohemolysin which combines with the red blood cells only at low temperatures, and hemolyzes them on subsequent raising of the temperature. If a suspension of red blood cells is added to such a serum, and the mixture is first chilled and then incubated at 37°, hemolysis takes place, whereas no hemolysis occurs if the preparation is incubated without previous chilling.

The following preparations were set up, tubes 2 and 3 being control tests:

1. Patient's serum 0.25 c. c. + patient's corpuscles 0.25 c. c. (1% suspension) 0° C. 1 hour, 37° C. 2 hours.
2. Salt solution 0.25 c. c. + patient's corpuscles 0.25 c. c. (1% suspension) 0° C. 1 hour, 37° C. 2 hours.
3. Patient's serum 0.25 c. c. + patient's corpuscles 0.25 c. c. (1% suspension) 37° 2 hours.

No hemolysis occurred in the test or in any of the control preparations. Even after standing in the ice-chest over night there was no hemolysis, though autoagglutination was evident. It was thought, then, that an autohemolysin might still be present, but its action on the red blood cells might be prevented by a lack of the necessary amount of complement, as was the case in the hemoglobinuric sera studied by Meyer and Emmerich (15). Accordingly, a similar series was set up with 0.1 c. c. of guinea-pig serum added to each tube. No hemolysis resulted. It seemed obvious, then, that the absence of hemolysis in the first experiment was not due to a lack of complement, and that probably no autohemolysin was present. In vivo experiments to demonstrate autohemolysis were not tried on account of the theoretical danger of causing intravascular agglutination.

Attempts were made to absorb out the autoagglutinin from the serum by digesting it with the homologous red blood cells, and interesting results were obtained. In the first experiment,

the digestion was carried out at 37° C. after an initial chilling, and in the second experiment at about 3° to 5° C.

1. Warm digestion. To 0.5 c. c. of the patient's serum were added 2.5 c. c. of a 10 per cent suspension of the patient's red blood cells. This mixture was kept at 3° C. for half an hour. Autoagglutination became very marked. The mixture was then warmed to 37° C. with resulting disappearance of the agglutination. The red cells were centrifugalized out, washed twice with warm salt solution, and suspended in salt solution. Chilling this suspension caused no agglutination, and hence the autoagglutinin had not been fixed, or remained fixed to the cells. The activity of the supernatant serum was tested by the addition of fresh red cells. Agglutination became marked on chilling this preparation. Therefore, the autoagglutinin was still present in the digested serum. The supernatant serum was again digested with the patient's red blood cells in the same way. These red cells were washed in warm salt solution, and the absence of any agglutinin fixed to the cells was demonstrated by their failure to become agglutinated on chilling them. The autoagglutinin was again demonstrable in the serum. One must conclude, therefore, that the autoagglutinin is not fixed to the cells, but remains free in the serum, when the digestion is carried out at body temperature.

2. Cold digestion. To 0.5 c. c. of the patient's serum were added 2.5 c. c. of a 10 per cent suspension of the patient's red blood cells. This mixture was kept at 3° C., and not allowed to become warm. Agglutination was marked throughout the experiment. The agglutinated red cells were centrifugalized out, and the supernatant serum tested for autoagglutinin. A preparation of this serum with fresh washed red blood cells showed no agglutination after prolonged chilling. Digestion with the homologous red cells in the cold had therefore absorbed the autoagglutinins completely from the serum. The sedimented red blood cells were washed twice with cold salt solution, and suspended in warm salt solution. The agglutination, which had been marked, disappeared in the warm solution, but reappeared on chilling this suspension again. The autoagglutinin, then, had not been removed from the cells by the cold washings. This suspension was warmed again, centrifugalized, and the supernatant fluid tested to see if the autoagglutinin had been liberated from the red cells on heating. This was found to be the case. The supernatant salt solution caused typical agglutination of fresh red blood cells in the cold. This solution did not cause agglutination of group 2 cells, nor of animal cells at 37°, and therefore did not contain normal isoagglutinin or heteroagglutinins. It contained the autoagglutinin isolated in purified form, and made possible a study of its activity undisturbed by other agglutinating substances in the serum. The sedimented red blood cells were washed twice with warm salt solution, and a suspension of them was chilled. No agglutination occurred, showing that the autoagglutinin had been entirely liberated from the red blood cells by warming.

By these experiments, therefore, it was shown that the autoagglutinin was not absorbed from the serum by digestion with red blood cells if the mixture were kept warm. If, however, digestion were carried out in the cold, the autoagglutinin was removed from the serum and fixed to the red blood cells. The physical or chemical process involved in the union was, however, a reversible one, and caused no permanent change in the red blood cells, since the autoagglutinin could be entirely liberated from the red blood cells by warming them, and since these red blood cells were now agglutinable by fresh serum.

These warm and cold absorption experiments were repeated, digesting the patient's serum with cells from an individual belonging to group 4. Exactly the same results were obtained. Removing the autoagglutinin for the patient's cells by cold digestion removed also that for group 4 cells, and vice versa.

The patient's serum from which the autoagglutinin had been absorbed was then tested to see if the ordinary normal isoagglutinin for group 2 cells had been removed also. This was found not to be the case. The absorbed serum caused marked agglutination of group 2 cells at 37° C., which was not increased by chilling. The isoagglutinin had not been affected by absorption of the autoagglutinin.

The isoagglutinin for group 2 cells was then absorbed from the patient's serum. Digestion of 0.5 c. c. of the serum with 0.1 c. c. of group 2 red blood cell "mush" at 37° for half an hour, absorbed completely the isoagglutinin. A preparation of this absorbed serum with fresh group 2 cells showed no agglutination when kept in the thermostat. However, when this preparation was placed in the ice-chest, a marked agglutination occurred, which disappeared on warming. This absorbed serum also agglutinated the patient's red blood cells, and cells from other individuals of groups 3 and 4, on chilling, with disappearance of the agglutination on warming. In this experiment, therefore, it was shown that the isoagglutinin for group 2 cells could be absorbed independently of the autoagglutinin, and that red blood cells of group 2, like those of groups 3 and 4, were susceptible to the action of the "cold" or "autoagglutinin."

It was also possible to demonstrate that the patient's serum possessed the property of causing "cold" agglutination of the red blood cells of other animals, in addition to ordinary heteroagglutination, and that the agglutination of these cells was brought about by the same substance which was active on human cells. This could be shown very easily with hen's cells, since no heteroagglutinins were present in the serum against the blood of the two hens used. Mixtures of this serum with washed hen's cells showed no agglutination at thermostat temperature, but marked agglutination at ice-box temperature. This agglutination broke up on warming the mixture, exactly as did the autoagglutination of human cells, and reformed on subsequent cooling.

Tests were also made with sheep, guinea-pig, rabbit, pig, and cat red blood cells. Heteroagglutinins were present in the serum for these species of cells. At first it was thought that these might be eliminated by using progressively increasing dilutions of serum for the tests, since the autoagglutinin, though much feebler than in the first experiments, was still present in fairly high concentration (about 1-100). The following tests were set up to determine the titer of the hetero-

agglutinins for these cells. After incubating at 37° for one hour, the degree of agglutination was noted, and the preparations were then chilled, and a second observation made. The following results were obtained:

Dilutions of patient's serum + sheep cells	Final serum dilution	37° 1 hr.	Chilled	37°
1-10	1-20	+++	++++	++++
1-20	1-40	0	++++	0
1-40	1-80	0	±	0
1-80	1-160	0	0	0

Dilutions of patient's serum + guinea-pig cells	Final serum dilution	37° 1 hr.	Chilled	37°
1-10	1-20	0	++++	0
1-20	1-40	0	+++	0
1-40	1-80	0	+	0
1-80	1-160	0	0	0

Dilutions of patient's serum + rabbit cells	Final serum dilution	37° 1 hr.	Chilled	37°
1-10	1-20	++++	++++	++++
1-20	1-40	+++	++++	++++
1-40	1-80	++	++++	+
1-80	1-160	+	+++	+

In the test with sheep cells, a dilution of serum of 1-20 sufficed to eliminate heteroagglutination. The "autoagglutinating" activity of the serum on sheep cells could then be demonstrated by chilling this mixture. This was better shown with the guinea-pig cells. Serum diluted 1-10 caused no heteroagglutination of the guinea-pig cells, while "autoagglutination" occurred with serum diluted up to 1-40. The results with the rabbit red blood cells are less definite, since heteroagglutination was present even with the serum diluted 1-80.

More conclusive results were obtained by digesting the patient's serum at 37° C. with sheep, guinea-pig, cat, pig, and rabbit red blood cells to remove the heteroagglutinins for these cells.

The patient's serum was digested with sheep cells (0.5 c. c. serum + 0.3 c. c. sheep cell "mush") at 37° for one hour. The cells were then removed by centrifugalization, and fresh sheep cells added. No agglutination occurred at 37°, showing that the absorption of heteroagglutinin was complete. On cooling this mixture, agglutination became marked, and on warming again it broke up exactly as did the autoagglutination of the patient's cells.

Heteroagglutinins for guinea-pig, cat, and pig cells were removed in the same way, and the activity of the "autoagglutinin" on these cells could then be demonstrated.

Heteroagglutinin for rabbit cells was also removed from the serum by digesting 0.5 c. c. of serum with 0.2 c. c. rabbit cell "mush" at 37° C. A preparation of this absorbed serum with fresh rabbit cells showed no agglutination at body temperature, but marked agglutination at ice-box temperature, which could be broken up on warming. That is to say, the heteroagglutinin was absorbed, leaving the autoagglutinin, which was active on rabbit cells. The absorbed serum was shown to still possess the autoagglutinating activity on group 4 red blood cells. Mixtures of this serum with guinea-pig cells and with sheep cells showed agglutination at 37°, demonstrating that the heteroagglutinins for these cells had not been affected by removing the heteroagglutinin for rabbit cells. It was further shown that this absorbed serum also contained the isoagglutinin for group 2 cells.

We then tried to absorb the autoagglutinin from this serum from which the heteroagglutinin for rabbit cells had been removed, by digesting it with 0.3 c. c. rabbit cell mush at ice-box temperature. The agglutinated cells were then removed by centrifugalization in the cold, and fresh rabbit cells were added to test the completeness of the absorption. Agglutination occurred when the mixture was chilled, showing that the serum was not exhausted. Three further digestions, each with 0.2 c. c. of rabbit cell mush, were necessary before absorption of the autoagglutinin was complete. We then tested the agglutinating activity of the serum for human group 4 red blood cells. Cooling this mixture caused no agglutination. Therefore, removal of the "autoagglutinin" for rabbit cells had also removed the "autoagglutinin" for human cells. That this disappearance of agglutinin was the result of a specific agglutinin absorption and not merely a non-specific mechanical removal by the relatively large quantity of cells used in the digestion, is indicated by the fact that the exhausted serum still retained, practically undiminished, its heteroagglutinins for guinea-pig and sheep cells, and its isoagglutinin for group 2 human cells. It seems probable, therefore, that the same substance was responsible for the "autoagglutination" of both rabbit and human cells.

The action of the autoagglutinin on the cells from different species of animals was also studied by means of the "purified agglutinin" already described. The autoagglutinin was absorbed from the serum by digestion in the cold with group 4 human red blood cells, and after washing the cells in cold salt solution several times, the autoagglutinin was liberated in warm salt solution. A solution of purified agglutinin was also prepared by absorbing it from the serum in the same way with rabbit cells. These solutions containing purified agglutinin were tested with rabbit, sheep, and guinea-pig red blood cells, and with human red blood cells of groups 2 and 4. No agglutination occurred in any of the mixtures at 37°. Agglutination became evident, however, in all of the preparations upon chilling, and disappeared upon warming them. These purified autoagglutinin solutions, then, contained no hetero- or isoagglutinin, as far as tested, but only the autoagglutinin which was shown to be active on all the species of red blood cells tested. This purified autoagglutinin, isolated by digestion of the serum with human red blood cells, was identical in its behavior with that obtained by means of animal (rabbit) red blood cells. One must conclude, therefore, that the autoagglutinin is a single substance, which, unlike iso- and heteroagglutinins is not specific, but is active on the red blood cells of different species of animals.

The action of the autoagglutinin was next tested on cells other than blood cells. An emulsion of epithelial cells from the urinary tract was prepared by centrifugalizing normal urine. As would be expected, the patient's serum did not cause any agglutination of these cells at 0° or at 37° C.

We attempted to study the chemical nature of the autoagglutinin, and particularly to determine whether or not it could be freed from proteid. The results obtained so far are inconclusive on account of the small amount of serum available. We found that, like other agglutinins, it was precipitated from the serum with the "euglobulin" fraction of the proteid by the addition of 36 volumes per cent of a saturated solution of ammonium sulphate. The fact that the agglutinated red blood cells, after being washed free from serum with cold salt solution, give up the agglutinin on warming, suggested that this method might be used to obtain the active substance in a relatively pure form, free from the ordinary proteid constituents of the serum.

Landsteiner and Jagić (16) have used a similar method in the study of the heteroagglutinin for goose red blood cells in beef serum. They found that this agglutinin is best absorbed in the cold, and is partially liberated on heating to 50° C. They digested a large volume of beef serum with thoroughly washed goose cell stroma in the cold, washed the agglutinated stroma in the cold, then suspended it in salt solution, and liberated the agglutinin by heating. This solution contained 0.2 per cent proteid, as compared with 6.6 per cent in the original serum. The agglutinin was precipitated from this solution with ammonium sulphate. However, the solution still contained considerable proteid independent of agglutinin, since most of the agglutinin could be removed by the addition of fresh stroma, leaving behind in the solution most of the substances giving the tests for proteid. They did not attempt further purification by repeating the procedure.

In making the tests for proteid, we used Heller's nitric acid test, since it was found to be much more sensitive for the proteids of serum than were the ordinary color reactions. Preliminary tests showed that normal horse serum in 1-2000 dilution gave a positive reaction with Heller's test, whereas Millon's and the biuret reaction were positive only in concentrations of 1-125, or higher.

Fresh red blood cells were used at first in the test but were found to be unsatisfactory. They could easily be washed free from serum, but after agglutination the mechanical injury incurred during the washings, together with the repeated warming and chilling, caused slight hemolysis, with liberation of sufficient hemoglobin to give a positive Heller's test. No better results were obtained by using red blood cells fixed in 1/2 per cent formalin. These cells absorbed agglutinin from the serum exactly as did fresh red blood cells. The different manipulations, however, caused some hemolysis of these cells also.

More satisfactory results were obtained by using stroma prepared by laking red blood cells belonging to group 4 with distilled water, and washing this red blood cell stroma several times. These laked red blood cells absorbed agglutinin from the serum in the cold, became agglutinated, and gave up agglutinin when warmed, with disappearance of agglutination, exactly as did fresh red blood cells. To 0.25 c. c. of thoroughly washed stroma was added 0.5 c. c. of the patient's serum. This was chilled in ice water half an hour. Macroscopic flocculi became visible in the suspension. After centrifugalizing cold the supernatant serum was pipetted off, and the stroma suspended in warm salt solution, in order to break up the clumps and to permit thorough washing. After the clumps were broken up the mixture was again chilled and centrifugalized. The supernatant salt solution was tested for proteid by Heller's test. After this had been repeated three times, the supernatant salt solution no longer gave a positive Heller's test. The stroma was then suspended in salt solution, and warmed to liberate the autoagglutinin, and the salt solution was centrifugalized free from stroma. This solution was shown to contain autoagglutinin by testing it with fresh group 4 cells, though the activity of the solution was not as marked as that of the original serum, and had evidently been weakened by the repeated manipulations. Heller's test was negative with this agglutinin solution, and the addition of ammonium sulphate to it caused no visible precipitate. By this method, therefore, we were able to obtain an agglutinating solution which gave a negative Heller's test, and hence contained less proteid than is contained in a 1-2000 dilution of serum. Though these results are suggestive, we cannot conclude definitely that this agglutinin is not a proteid, since the limited quantity of serum available did not permit of further tests.

In order to differentiate this autoagglutination more clearly from rouleaux formation, a similar study was made of this phenomenon. This work is still incomplete, and a more detailed report of it will appear in a later paper. Certain differences in these two phenomena may be mentioned here. As pointed out by Decastello and Sturli (17), and by Sellards (3), and confirmed in our experiments, serum is able to cause rouleaux formation only in high concentrations. In the sera which we studied, a dilution of 1-4 was sufficient to destroy this activity. The autoagglutinating serum, on the other hand, was active after dilution to 1-500. These authors also point out that the property of the serum of stimulating rouleaux formation, and that of the red blood cells of becoming clumped in rouleaux is very unstable, and disappears within a few hours, or, at most, a few days. This was true in our experiments with rouleaux-forming serum, while the serum causing autoagglutination has remained active, with but slight diminution in strength, for several months. Fresh cells were not necessary for demonstrating autoagglutination. Heating the rouleaux-forming serum to 65° for 1/2 hour increased definitely its activity, as noted by Sellards (3), while heating the autoagglutinating serum to this point entirely destroyed its activity.

In our experiments, the formation of rouleaux seemed not to be affected by raising or lowering the temperature of the mixture, as was the agglutination of red blood cells by the autoagglutinating serum. After preparations showing rouleaux formation had stood at room temperature for several hours, the rouleaux broke up much as did the clumps of autoagglutinated red blood cells. This breaking up of rouleaux, however, occurred at low temperatures as well as at body temperature and, after it once occurred, no reformation of the rouleaux could be obtained. We found that the rouleaux stimulating substance could not be absorbed from the serum even by

repeated digestions with large quantities of red blood cells, whereas the autoagglutinin could readily be absorbed. Certain points of resemblance between these two active substances were brought out in our studies. Both were active on cells from other individuals. Both substances were precipitated from the serum with the "euglobulin" by the addition of 36 volumes per cent of saturated ammonium sulphate solution. Both substances remained in the serum after dialysis in a collodion sac. However, in the case of the rouleaux-forming serum, dialysis could only be carried out for 24 hours, because the activity of this serum disappeared on longer standing. From these observations it seems clear that autoagglutination and rouleaux formation are entirely different phenomena.

DISCUSSION

The question then came up, is the phenomenon of autoagglutination in this patient's blood in any way related to the disease for which she entered the hospital? To settle this point, we studied the blood again during convalescence, shortly before her discharge from the hospital. Red blood cell counts could then be made without using warm solutions. Red blood cells and serum were obtained as before. Progressive dilutions of serum were made as previously and red blood cells added. Agglutination occurred only in dilutions under 1-16, and only at temperatures below 11° C. To again test out this point, other specimens of serum and red blood cells were obtained two months after the patient had recovered from her pneumonia. This time care was taken to keep the blood warm while it was clotting, and until the serum was removed, to prevent any fixation of the autoagglutinin to the cells in the clot, with resulting reduction in the strength of the serum. Autoagglutination again occurred in dilutions up to 1-16, and at temperatures below 15° C. At this time a few drops of blood were obtained from a daughter of the patient, and a similar autoagglutinin was found in this blood. It appeared to be somewhat feebler than that present in the mother's serum, but the amount of blood obtained was insufficient for further tests. It is obvious, therefore, that this peculiarity was quite independent of the disease from which the patient was suffering, and was an individual peculiarity, apparently hereditary. The increased strength of the agglutinin during the early part of her disease may have been related in some way to the infection, or may have been purely accidental.

SUMMARY

Autoagglutination, or agglutination of red blood cells by serum from the same individual, was observed in the blood of a patient admitted to the hospital on account of a bronchopneumonia associated with chronic mitral endocarditis.

Agglutination occurred only at low temperatures (below 22° C.), and broke up if heated to body temperature. Agglutination could be reproduced by again chilling the same preparation.

This serum caused similar agglutination of red blood cells from other individuals of the same blood group (group 3), and also of group 4. (It contained ordinary isoagglutinins active at body temperature for cells of members of groups 1 and 2.) The cells of the patient washed free from serum showed no tendency to agglutination, and behaved exactly as did cells from other individuals of group 3. Hence the phenomenon depended solely on a peculiarity of the serum, and not of the cells.

The active substance in the serum had many of the properties of an ordinary agglutinin. It was active in fairly high dilution (up to 1-500). It resisted heating to 60° C. for 1/2 hour, but was destroyed at 65° C. It remained active after preservation in the ice-box for several months. It was not dialyzable. It was not removed by extraction with chloroform. It was precipitated with the "euglobulin" by 36 volumes per cent of saturated ammonium sulphate solution. It was absorbed from the serum during the process of agglutination (at low temperatures).

It was entirely distinct from the ordinary isoagglutinins in the serum, since either one could be removed from the serum, leaving the other intact.

The autoagglutinin differed from ordinary agglutinins in the following ways: 1. It was active only at low temperature, the agglutination breaking up on warming. 2. It was absorbed from the serum only at low temperature, and was liberated from the cells on warming. 3. It was active on red blood cells from all of the different species of animals with which it was tested (man, rabbit, guinea-pig, hen, sheep, cat, and pig). That the same substance was concerned in the agglutination of human cells and of cells from these different animals, and that it was distinct from the ordinary heteroagglutinins, which were also present in the serum, was shown by the absorption tests already described.

An attempt was made to study the chemical nature of the autoagglutinin, especially its relation to proteid, but the results were inconclusive. By liberating the agglutinin from washed, agglutinated red blood cell stroma in warm salt solution, a solution of agglutinin was obtained which gave a negative Heller's test and showed no precipitate on the addition of ammonium sulphate. This solution, therefore, contained less proteid than is contained in a 1-2000 dilution of horse serum. Further tests were impossible on account of the small supply of serum available, and the weakening of the autoagglutinin caused by the manipulations.

No autohemolysin was present in the serum.

A similar study of rouleaux formation was made in order to differentiate it more clearly from autoagglutination. The substance causing rouleaux formation resembled the autoagglutinin in that it, also, was active on cells from other individuals. Both substances were precipitated from the serum with the "euglobulin," and neither was dialyzable. Unlike the autoagglutinin, the rouleaux-forming substance was active only in concentrated serum. Its activity rapidly disappeared upon standing, and fresh cells were necessary for the formation of rouleaux. Rouleaux formation occurred equally well at high or low temperatures. Heating the serum to 65° C. increased its rouleaux-forming power. This substance was not absorbed

from the serum by the cells in the process of rouleaux formation.

The presence of the autoagglutinin was probably not related in any way to the disease from which the patient was suffering. It persisted with slight variation in strength for a period of two months' observation, and was found to be present in the serum of a daughter of the patient. Hence it was probably not a pathological phenomenon, but an individual, hereditary peculiarity.

REFERENCES

1. Minot, G. R.: Methods for testing donors for transfusion of blood, and consideration of factors influencing agglutination and hemolysis. Boston M. and S. J., 1916, CLXXIV, 667-674.

2. Fishbein, M.: Isoagglutination in man and lower animals. J. Infect. Dis., 1913, XII, 133-139.

3. Sellards, A. W.: The effect of heated serum on rouleaux formation of red blood corpuscles. Bull. Johns Hopkins Hosp., 1908, XIX, 271-274.

4. Reitmann, A.: Ueber Bluterbrechen bei Lebercirrhose. Wien. klin. Wchnschr., 1890, III, 404-407.

5. Ascoli, M.: Isoagglutinine und Isolysine menschlicher Blutsera. Münch. med. Wchnschr., 1901, XLVIII, 1239-1241.

6. Klein, A.: Beiträge zur Kenntnis der Agglutination rother Blutkörperchen. Wien. klin. Wchnschr., 1902, XV, 413-418.

7. Landsteiner, K.: Ueber Beziehungen zwischen dem Blutserum und den Körperzellen. Münch. med. Wchnschr., 1903, L, 1812-1814.

8. Landsteiner, K.: Ueber Serumagglutinine. Münch. med. Wchnschr., 1902, XLIX, 1905-1908.

9. Hektoen, L.: Phagocytosis of red corpuscles. J. Infect. Dis., 1906, III, 721-730.

10. Hektoen, L.: Isoagglutination of human corpuscles. J. Infect. Dis., 1907, IV., 297-303.

11. Rous, P.: Personal communication.

12. Ottenberg, R., and Thalhimer, W.: Studies in experimental transfusion. J. Med. Research, 1915, XXXIII, 213-229.

13. Moss, W. L.: A simplified method for determining the isoagglutinin group in the selection of donors for blood transfusion. J. Am. M. Ass., 1917, LXVIII, 1905-1906.

14. Donath, J., and Landsteiner, K.: Ueber paroxysmale Hämoglobinurie. Münch. med. Wchnschr., 1904, LI, 1590-1598.

15. Meyer, E., and Emmerich, E.: Ueber paroxysmale Hämoglobinurie. Deutsches Arch. f. klin. Med., 1909, XCVI, 287-327.

16. Landsteiner, K., and Jagić, N.: Ueber die Verbindungen und die Entstehung von Immunkörpern. Münch. med. Wchnschr., 1903, L, 764-768.

17. Decastello, A. v., and Sturli, A.: Ueber die Isoagglutinine im Serum gesunder und kranker Menschen. Münch. med. Wchnschr., 1902, XLIX, 1090-1095.

A SIMPLE METHOD FOR THE DETERMINATION OF VENOUS PRESSURE[1]

By N. WORTH BROWN, M. D.

(From the Medical Clinic of The Johns Hopkins Hospital)

A convenient instrument for the measurement of pressure within peripheral veins may be easily constructed from an ordinary mercurial manometer. The apparatus consists of a single-limb manometer in which water, carbon tetrachloride (Carbona) (Sp. Gr. 1.5) or bromoform (Sp. Gr. 2.5) is substituted for mercury. To the manometer is connected a small, saddle-shaped cup, 2 cm. in diameter, covered with the thinnest rubber tissue obtainable. This membrane must be loosely applied and should permit free oscillation without tension. A rubber bulb with thumb-screw compressor regulates the pressure within the manometer. The use of carbona or bromoform instead of water is advocated because of higher specific gravity and lower viscosity. Carbona is preferred for routine observations. The readings are easily reduced to water pressure.

The principle employed is that described by von Basch in 1876 for the determination of arterial pressure.[2] Oliver[3] and Sewall[3] have published studies on venous pressure obtained in a somewhat similar manner but using a spring pressure gauge applied directly over the vein. The manometer devised and used by Hooker[4] and later by Clark[5] has been used for some time in this institution and the observations made with it have demonstrated the value of venous pressure estimations in the clinical study of cardio-vascular and pulmonary disease.

[1] Presented before The Johns Hopkins Medical Society, May 21, 1917.

The method here described differs from that used in recording venous pressures with the Hooker manometer. With the

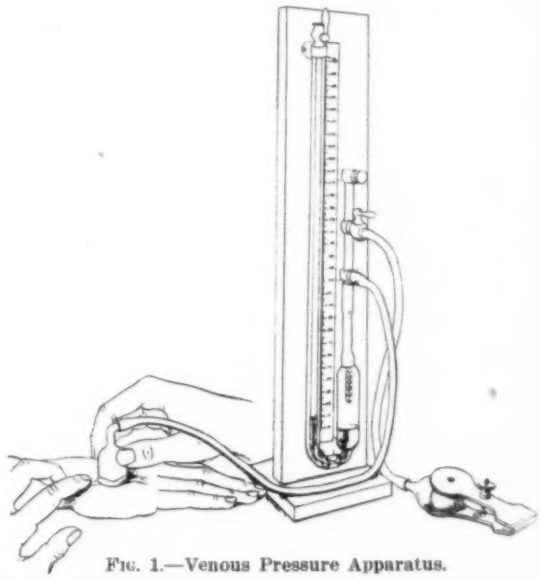

FIG. 1.—Venous Pressure Apparatus.

latter, a glass cup is cemented to the skin and the pressure necessary to obliterate the vein is determined by direct inspection through the cup, of the collapsed vessel; in this, the pres-

sure required to prevent the return flow is measured and the appearance of a venous "wave" marks the reading point. It is desirable to use a prominent superficial vein in which the valves are effective. Pressure in the manometer is raised several centimeters and the cup, or capsule, is placed upon the vein with sufficient pressure to obstruct the return flow. The vein on the proximal side of the capsule is emptied by stroking in the direction of venous flow. The pressure in the manometer is allowed to fall by opening the needle valve. When the venous pressure equals the manometer pressure the vein above the capsule will rapidly fill. A reading at this time will give the approximate venous pressure.

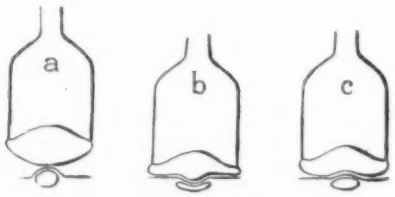

FIG. 2.—(a) Before pressure is applied. Pressure in the vein is greater than within the capsule.
(b) Capsule pressed downward. Lumen of the vein obliterated. Pressure in the capsule is greater than in the vein.
(c) Capsule is slowly raised. When the pressure in the vein equals that within the capsule, blood will pass through the partly compressed vessel. The manometer reading at this point indicates the venous pressure.

After this preliminary observation the capsule is inflated but not distended (0.5 cm. water pressure) and the manometer valves are closed. The capsule and manometer now form a closed circuit. Repeated readings can be made by pressing down the capsule, stripping the vein and slowly raising the capsule, observing the height of the column in the manometer when the venous flow first returns. If reasonable care is exercised, the variations should not exceed one centimeter. Mechanical factors, which may under certain conditions influence results thus obtained, are constant and so insignificant that for clinical purposes they may be disregarded. It is important that the capsule be so adjusted that its margin does not compress the vein. As with all methods of estimating venous pressure the vein employed must be at the heart level.

For the fluid manometer may be substituted an aneroid adjusted to record low pressures in centimeters of water.

Simultaneous observations made with Hooker's venous manometer and with this apparatus give approximately the same results. Normal pressures, so far observed, when taken upon individuals resting quietly in the recumbent position with the arm extended and the hand at the heart level give readings between 3 and 9 cm. H_2O. Two cases of essential hypertension had pressures within normal limits. A well compensated aortic stenosis showed an average of 8.1 cm. Two patients with valvular lesions and auricular fibrillation had venous pressures ranging from 12 to 18 cm. of water. An uncompensated aortic regurgitation during the periods of dyspnœa showed a pressure of 26 cm. A patient with obstruction in the superior vena cava gave a peripheral pressure of 14.6 cm., while the thoracic, at the same level, serving as a collateral, showed a pressure of 12.7 cm. Thrombosis of the left subclavian vein produced a pressure of 30 cm. in the left hand, whereas on the unaffected side it measured only 16 cm.

From these limited observations we are led to believe that readings with this instrument of 10 cm., or lower, represent normal venous pressures. In cardiac lesions pressures between 12 and 18 cm. suggest moderate decompensation, whereas constant pressures of from 20 to 30 cm., or over, indicate venous stasis and serious myocardial insufficiency.

The advantages of the method described are obvious. The determinations are equal in accuracy to any method except that which depends upon the introduction of a canula. The simplicity of the apparatus, its ease of manipulation, the rapidity with which observations can be made and an unmistakable reading-point, will commend its use for clinical purposes.

REFERENCES

1. Janeway: The Clinical Study of Blood Pressure, 1904, p. 43.
2. Oliver: Am. Jour. Physiol., 1898, XXII, 51; Am. Jour. Physiol., 1898, XXIII, 5.
3. Sewall: Jour. Am. Med. Assn., 1906, XLVII, p. 1279.
4. Hooker and Eyster: Johns Hopkins Hosp. Bull., 1908, XIX, p. 274. Hooker: Am. Jour. Physiol., 1911, XXVIII, 5, p. 235; Am. Jour. Physiol., 1914, XXXV, 1, p. 73; Am. Jour. Physiol., 1916, XL, 1, p. 43.
5. Clark: Arch. Int. Med., 1915, XVI, p. 587.

ABSTRACTS OF PAPERS

Representing Work Done in The Johns Hopkins Hospital, but Published or to be Published Elsewhere than in the Bulletin. Prepared by the Authors.

THE MAINTENANCE DIET IN DIABETES MELLITUS AS DETERMINED BY THE NITROGEN EQUILIBRIUM

By HERMAN O. MOSENTHAL and SAMUEL W. CLAUSEN
(From the Medical Clinic of The Johns Hopkins Hospital)

In the treatment of diabetes mellitus, there are two guiding principles which determine the caloric value of the diet. In the first place, the quantity of carbohydrates, proteins and fats offered the patient must be within his carbohydrate tolerance; that is, the diet must be so regulated that the urine remains sugar-free. It is generally acknowledged that under these circumstances the disease itself is treated in the most effective manner. Secondly, a diet of sufficient caloric value should be offered the patient, so that his health and strength may be maintained at a normal level. It is readily appreciated that these two guiding principles of treatment are diametrically opposed to one another in many respects. The one demands a restricted diet, and in many instances, undernutrition; the other calls for a larger amount of food. The first aims at treat-

ing the disease, diabetes mellitus; the second attempts to conserve the nutrition of the patient. The neglect of either factor may entail undesirable results.

During the past years, emphasis has been continually placed upon the dietary restriction and the prevention of glycosuria. Previously, on account of lack of full appreciation of the results which could be obtained by a more drastic curtailment of the food calories, this idea was not pushed to its logical conclusion of controlling the glycosuria of nearly every diabetic patient. Through the efforts of F. M. Allen, by systematic and radical reduction in the food, this may be easily accomplished in most cases.[1] The widespread use of these very limited diets has brought up the question of how little the individual may eat and yet remain physically and mentally fit. It is the object of the present paper to furnish at least a partial answer to this problem.

The standard for maintenance for the diabetic may be sought in one of two criteria; first, the caloric requirement, and second, the nitrogen equilibrium. The caloric requirement may be readily ascertained according to the height-weight formula of Du Bois and Du Bois.[2] Food administered in accordance with this standard [3] should satisfy all theoretic demands. The nitrogen equilibrium represents the lowest possible diet which could be exacted of any patient. Food, under these circumstances, results in the conservation of the protein tissues, but does not necessarily prevent the loss of fat. This principle has been applied in the treatment of obesity; it was successfully used in the prolonged dietetic experiments of Chittenden on normal people, and is employed here. No living being can afford to lose muscle and glandular tissue indefinitely. How far the fat store of any individual may be depleted with advantage is another question. There is much to be said in favor of allowing the diabetic to become thin, so that his metabolism may be established at a lower level, as has so frequently been urged, but it should be distinctly appreciated that this loss of weight should occur in the fats and not in the vitally necessary proteins. It is with these ideas in mind that the nitrogen equilibrium has been chosen as the lowest possible food standard by which diabetics may be maintained in a state of physical and mental well-being over longer periods.

Table 1 presents a summary of some of the cases studied. All of these patients were given diets of the same relative proportion of fats and proteins. These two food substances were maintained equal to each other, gram for gram, as nearly as possible. Only such carbohydrates were given as were unavoidably present in the green vegetables. In this way, these patients received diets which made a comparison as to the effect on the nitrogen equilibrium possible. From the table it may be noted that diabetic patients may be established in nitrogen equilibrium by a carbohydrate-free diet having a caloric value equal to the standard total caloric requirement. In many instances, this may be accomplished at a considerably lower level of feeding. The lowest diet which will conserve the physical and mental efficiency of the diabetic is that which maintains the nitrogen equilibrium. A rough estimate for clinical purposes of what constitutes a maintenance ration for the diabetic on a carbohydrate-free diet is from 1500 to 2000 calories. In adjusting the value of the diet, it should be borne in mind that women and small individuals generally require less food than men and larger individuals.

TABLE 1

CALORIC REQUIREMENT NECESSARY TO PRODUCE NITROGEN EQUILIBRIUM IN CASES OF DIABETES MELLITUS, AS COMPARED WITH THE NORMAL METABOLISM OF INDIVIDUALS OF THE SAME AGE AND SEX. A SUMMARY OF SOME OF THE CASES STUDIED

Case	Age	Sex	General condition	Calories per hour per square meter of body surface: Highest at which N equilibrium was not obtained	Calories per hour per square meter of body surface: Lowest at which N equilibrium was obtained	Calories per hour per square meter of body surface: Normal metabolism*	Caloric requirements necessary to establish N equilibrium as compared with normal metabolism
1. Period 1.	38	M.	Very poor	41.6	47.2	43.7	8 per cent higher
Period 2.	..	...	.....	41.6	47.4	43.7	8 per cent higher
2.....	35	F.	Fair	31.6	39.7	40.6	Unchanged
3.....	43	M.	Poor	36.3	43.7	43.7	Unchanged
4.....	56	F.	Normal	18.2	27.0	36.0	25 per cent lower
5.....	26	M.	Fair	....	35.9	43.7	18 per cent lower
6.....	35	M.	Normal	33.8	28.2	43.7	28 per cent lower
7.....	41	M.	Normal	45.6	49.1	43.7	12 per cent higher
8. Period 1.	13	M.	Normal	49.7	39.5	54.9	28 per cent lower
Period 2.	..	...	.....	37.7	51.7	54.9	6 per cent lower
9.....	12	F.	Poor	36.4	....	....	?

* Basal metabolism according to F. C. Gephart and E. F. Du Bois (Arch. Int. Med 1916, XVII, 902), plus 10 per cent to allow for the specific dynamic action of the diet.

Certain other facts were developed in the course of this study which are not brought out in the table, but which may be briefly summarized as follows: The factors which determine the dietary level at which a diabetic maintains a nitrogen balance are apparently very numerous and not fully determined; glycosuria at times, and infections, even of very slight degree, may necessitate a higher diet to bring about the desired result. A marked assimilation of nitrogen may occur in diabetics while on a carbohydrate-free diet.

THE EFFECT OF DIET ON BLOOD SUGAR IN DIABETES MELLITUS. (Abstract)

By HERMAN O. MOSENTHAL, SAMUEL W. CLAUSEN and ALMA HILLER

(From the Medical Clinic of The Johns Hopkins Hospital)

Aside from its physiological interest, it was hoped that this investigation would yield information which would enable the clinician to interpret blood-sugar values taken at any time of the day. The blood sugar was determined at hourly intervals in cases of diabetes mellitus. The patients were ordered diets which were adjusted to the therapeutic needs of the individual,

[1] Allen, F. M.: Boston Med. and Surg. Jour., 1915, CLXXII, 241.

[2] Du Bois, D., and Du Bois, E. F.: Arch. Int. Med., 1916, XVII, 863.

[3] Gephart, F. C., and Du Bois, E. F.: Arch. Int. Med., 1916, XVII, 902.

that is, they were "carbohydrate-free," containing no starch except that present in green vegetables, or, except in a very few instances, limited in starch content so that the glycosuria was held in abeyance or at a low level. The results obtained under these circumstances, while they do not exhaust the subject from the physiological or pathological physiological point of view, are applicable to the practical interpretation of blood sugars in the treatment of diabetes mellitus.

TABLE 1

SUMMARY OF THE HOURLY DETERMINATIONS OF BLOOD SUGAR IN CASES OF DIABETES MELLITUS ON A CARBOHYDRATE-FREE DIET, OR ONE CONTAINING A MODERATE AMOUNT OF STARCH. IF THERE IS A RISE OF BLOOD SUGAR IN THE COURSE OF THE DAY, THE MAXIMAL VALUE REACHED ONE OR TWO HOURS AFTER BREAKFAST IS USUALLY NOT EXCEEDED TO ANY MARKED DEGREE AFTER LUNCH OR SUPPER. THERE FREQUENTLY IS A DIMINUTION IN THE GLYCEMIA IN THE AFTERNOON AND EVENING.

	Blood sugar per cent					
Fasting	After breakfast		After lunch		After supper	
	Maximal	Minimal	Maximal	Minimal	Maximal	Minimal
.18	.18	.17	.17	.13	.17	.11
.45	.45	.45	.45	.45	.45	.45
.23	.23	.23	.23	.23	.23	.19
.33	.33	.33	.33	.32	...	.28
.18	.18	.18	.19	.18	.18	.18
.17	.17	.17	.18	.18	.18	.18
.12	.19	.16	.20	.16	.16	.14
.15	.19	.15	.19	.11	.17	.15
.14	.16	.16	.18	.16	.16	.16
.13	.16	.13	.14	.08	.18	.15
.16	.25	.23	.23	.22	.26	.22
.14	.17	.14	.17	.17	.17	.15

The maximal percentage of blood sugar occurring in diabetic individuals on a carbohydrate-free diet, or one containing a moderate amount of starch, may be obtained one to two hours after breakfast. The glycemia may rise somewhat higher after lunch or supper, but never to any marked degree. On the other hand, the blood sugar may fall considerably in the afternoon and evening hours, leading to erroneous interpretations if taken only at this time of the day (Table 1).

In diabetic cases there is a tendency for the blood sugar to remain constant throughout the day while on a protein-fat diet, if the fasting blood sugar is high; on the other hand, if the fasting blood sugar is low, that is, if it has been reduced by previous dietetic treatment, there is an increase in the glycemia after carbohydrate-free food, which may become very marked (Table 1). This leads to the conclusion that diabetic patients, by raising their fasting or basal blood sugar percentage, tend to adjust their carbohydrate metabolism in such a manner that they are able to utilize the food offered them to better advantage. It may be desirable, therefore, not to attempt to reduce the blood sugar to a normal value in all cases of diabetes mellitus.

A RARE TYPE OF BLADDER ULCER: FURTHER NOTES, WITH A REPORT OF EIGHTEEN CASES[1]

By GUY L. HUNNER, M. D., Baltimore, Md.

(Abstract from the Journal of the American Medical Association, 1918, Vol. LXX, 203.)

The author refers to his original publication in The Transactions of the Southern Surgical and Gynecological Association in 1914, in which eight cases were described of a type of bladder ulceration hitherto unreported.

The lesion is a chronic infiltration of all coats of the bladder wall, usually of broad extent in the vertex or free portion of the bladder, and presenting one or more minute superficial ulcers in the mucosa layer.

The urine is always macroscopically clear but on carefully pipetting and centrifuging, one can find microscopically a few leukocytes and a few erythrocytes. Culture of the urine is always negative.

The symptoms are those of an intense and most painful cystitis, usually having extended over a period of many years, and being uninfluenced or only partially allayed by the usual methods of cystitis treatment.

In addition to the bladder pain, strangury, and frequency of voiding, there are often referred pains to the intestines, and especially to the rectum, to the lateral pelves and hips, and down the thighs, and to the vagina and perineal region.

The etiology of this type of bladder inflammation is still a matter for investigation. In one of the 18 cases there was a history of a colon bacillus cystitis following an Alexander operation 18 years previously. With this exception, none of the cases could be traced to a past operation, catheterization, childbirth, or gonorrhea, the frequent forerunners of a chronic cystitis. The fact that many of the patients refer the beginning of their symptoms to childhood or early adult life makes one think of the possibility of a focal infection as the etiological factor. The fact that the lesion is found in the vertex or free portion of the bladder rather than in the base, where are found the chief blood and lymph connections, is probably an argument against the focal infection theory.

As stated above, cultures from the urine are always sterile. In several cases the fresh tissues taken at operation have been macerated and used for anaërobic cultures with uniformly negative results. Many slides have been prepared with various stains in an attempt to demonstrate microorganisms in the tissues, but with negative results.

The successful treatment of these cases depends upon a complete excision of the entire area of infiltration, and this often involves the major portion of the bladder. One is surprised after repeated careful cystoscopy, which usually reveals an apparently superficial inflammatory condition limited to a comparatively small portion of the vertex of the bladder, to find at operation a widespread edema of the bladder mucosa.

[1] Paper read in the Section on Obstetrics, Gynecology, and Abdominal Surgery at the sixty-eighth annual session of the American Medical Association in New York City, June 7, 1917.

subtended by thickening and infiltration of all coats of the bladder.

The excision must include the entire edema area, and the histologic study of the removed specimen shows that the chronic inflammation of the walls is coextensive with the area of edema. This explains the futility of local treatments.

The past failure of urologists to discover this lesion in spite of the patient's intense and persistent bladder symptoms has been due chiefly to three factors. First, careless urinary analyses have overlooked the few leukocytes and erythrocytes present in an otherwise normal urine. Seeing a macroscopically clear urine and failing to grow a culture has led to a careless and negative microscopic examination, or on finding a few leukocytes and erythrocytes these have been dismissed as of no significance. Second, the minute and superficial character of the ulcer portion of the lesion has caused it to be entirely overlooked or its importance to be ignored. Third, the usual location of the lesion in the vertex or on the anterior wall back of the symphysis is the most difficult portion of the bladder to explore by either the Nitze or Kelly methods of cystoscopy.

The extra-vesical or referred pain phenomena have led to many errors of diagnosis, 9 of the 18 patients having had a total of 16 operations directed toward the relief of their symptoms. These operations were largely futile because of a failure to make a proper diagnosis.

PROCEEDINGS OF SOCIETIES

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY

DECEMBER 3, 1917

1. Exhibition of a Case of Psoriasis. DR. LLOYD W. KETRON.

This case is presented to the Society because of the remarkable shape of the lesions. The patient is a young man, aged 29, and is engaged in work of a clerical nature. He has had psoriasis for four years. The disease has only once entirely disappeared from his body, remaining away for about four months. It was during the second attack that the lesions took on the unusual contour which they now present. During the first attack, they were of the discoid type.

At the present time (see photograph), the disease is rather widely disseminated over the entire body. The most striking lesion is a band on the left side, about an inch and a half wide, extending from beneath the axilla with a serpentine contour down to the pubic region. There is a similar band on the right side of the body. On the thighs, and back, some of the lesions, although much smaller, are also coiled in a snake-like manner. Besides this serpentine arrangement, there are a few lesions of the discoid, or guttate variety.

The usual types of psoriasis are the punctate, guttate, discoid, and irregularly shaped patches of larger size. Occasionally, there is an annular form, and sometimes, when the lesions coalesce, a gyrate configuration may result. I have, however, never seen lesions showing such a clear-cut serpentine contour, as the ones in the present case. According to the patient's history, these bands were formed from the confluence of round patches, which appeared in the lines which the present lesions have now assumed.

In answer to Dr. Brown's question as to the treatment of psoriasis: there is nothing radically new at the present time, that promises to be of special value. Chrysarobin ointment still seems to be our most efficient remedy. It is, however, very unpleasant for the patient to use, because it stains all the clothing, and frequently sets up a dermatitis on the normal skin.

The injection of autogenous serum was rather enthusiastically used for a while, but the work of Dr. Willock in our department gave practically negative results. Interesting metabolic studies in psoriasis cases have been lately carried on by Schamberg and his associates in Philadelphia. They have shown that there is a nitrogen retention, and have claimed good results in treatment by giving a low protein diet.

The X-ray is of very great value in cases which have just a few very persistent chronic patches of psoriasis. These patches usually respond very quickly to one or more suberythema doses.

2. The Use of Relaxation Incisions in Dealing with Extensive Unstable Scars. DR. JOHN STAIGE DAVIS.

Introduction.—The treatment of tightly stretched unstable scars, which frequently break down, has long been a source of worry to the surgeon and of distress to the patient.

This type of scar usually follows extensive deep burns or loss of tissue by trauma where the wound has been allowed to heal by the slow process of cicatrization, without the aid of skin-grafting or of plastic operation.

The original wounds are always large and usually involve the entire circumference of a part, such as the leg or thigh, or occasionally the calvarium. In other words, the scar surrounds and compresses the part.

Some of the scars are bluish red with fine superficial vessels; others are pale and seem to have little or no blood supply. Frequently there are superficial ulcers of various sizes scattered over the surface. The scars are as unstable as wet tissue paper and the slightest injury will start an ulcer that will take weeks to heal.

There is little resistance to trauma or infection, and an area that is healed, in a very short time and without any apparent cause, may break down entirely; or multiple ulcers may develop.

A number of these cases have come under my care, and for a long time gave me much trouble. After using many methods with little success, it occurred to me to try relaxation incisions and to graft the defects thus made.

Technic.—It is preferable that the area be entirely healed before the incisions are made, but in some instances where the cicatrization of the superficial ulcers has been extremely sluggish I have not waited for complete healing, but have operated as soon as the granulations have been brought into a healthy condition. Before operation in the unhealed cases, after the granulations have become healthy, the part is put up in a dressing kept wet with normal salt solution for 24 hours. The granulations are then painted with tincture of iodine and the surrounding scar is cleaned with ether and alcohol.

Not infrequently the relaxation incisions can be made after infiltration with a local anesthetic, such as Schleich's solution, or one-half per cent novocain. In other instances a general anesthetic is advisable, especially if large immediate Thiersch grafts are to used to cover the defect.

On an arm or leg long incisions should be made, parallel to the long axis of the part, down to the deep fascia, or down to healthy tissue if the destruction has been deeper than the fascia. Three relaxation incisions are usually sufficient for a limb and result in gaping wounds.

Remarks.—The immediate spreading of each relaxation incision varies with the tightness of the scar. In some instances it is as much as 2.5 to 3 inches at the center of the incision. The spread of the first incision is, of course, the widest.

After the tension has been relieved the appearance of the scar tissue between the incisions soon changes, and instead of retaining the thin, glossy, mottled look, the tissue seems to thicken and to acquire greater stability. This improvement is much more marked after a few days.

When the scar is stretched over a broad expanse of bone, such as the skull, as many horizontal incisions as may be necessary should be made down to the periosteum. The spread of relaxation incisions over bone is not so marked as over soft parts, and some undercutting may have to be done. In these cases the beneficial effect is more marked after a week or two, but in the end the result is very satisfactory.

In some cases of very long standing the tissue exposed by relaxation incisions has atrophied from pressure and lack of use and has such a poor blood supply that immediate grafting is unwise. In these cases it is advisable to wait for several days until the wounds are lined with granulation tissue and then to apply the grafts.

In other instances immediate grafting is justified, but this point must be determined at the time of the operation.

It is extraordinary to note the rapidity of healing of the superficial ulcers after the relaxation incisions are made.

I have used only small deep grafts and Thiersch grafts on the defects caused by the relaxation incisions. These grafts have been so far entirely satisfactory, however, that there seems to be no reason why grafts of whole-thickness skin should not be used in cases where this type of graft may be necessary.

There has been no recurrence of superficial ulceration in any case where the tension has been completely relieved by the method described above.

Conclusions.—By the use of relaxation incisions with immediate or subsequent skin grafting of the defects, large unstable scars can be firmly healed in a comparatively short time, and patients who have been incapacitated for many months can resume their usual occupations.

I have used this method on a number of cases, with uniform success, and feel that it is a rational procedure and well worth trying.

3. Observations on Bird Malaria and the Pathogenesis of Relapse in Human Malaria. LIEUT.-COLONEL EUGENE R. WHITMORE, Army Medical School, Washington, D. C.

Published in the March number of the BULLETIN.

DECEMBER 17, 1917

1. The Preparation of the U. S. Army Triple Typhoid Vaccine (Illustrated with Moving Pictures). MAJOR C. G. SNOW, Army Medical School, Washington, D. C.

To be published in a later number of the BULLETIN.

2. Recent Work on the Differentiation of the Paratyphoid Group in Relation to Disease in Man. DR. CHARLES KRUMWIEDE, Department of Health, New York City.

DISCUSSION

DR. W. W. FORD.—Of course it is very gratifying to me to find that a distinction between the various types of paratyphoid bacilli made out so many years ago has been confirmed by Dr. Krumwiede in a manner which is more comprehensive than that shown in the original suggestion.

There are many extremely interesting features about this group. In the original work upon the paratyphoid organisms, I was impressed by the fact that practically all of the paratyphoid cultures rendered milk alkaline if you gave them sufficient time to act. That is to say, the old distinction between paratyphoid A and B, based upon the production of permanent acidity in milk in the one group, and the loss of acidity and production of alkalinity in the other, was not a valid distinction. The two groups could be differentiated, however, by the use of the higher polysaccharids, such as arabinose and xylose. One reason for the reported stability of *Bacillus enteritidis* of Gärtner is that so few cultures of this organism are available for study. The majority of those found in America for instance, are derived from a culture sent to The Johns Hopkins many years ago by Dr. Durham, of Cambridge, England. It is interesting to note how Dr. Krumwiede's studies have enabled bacteriologists to trace the origin of many of these strains back to their original animal host.

BOOKS RECEIVED

Obstetrics for Nurses. By Charles B. Reed, M. D. 134 illustrations. 1917. 12°. 374 pages. C. V. Mosby Company, St. Louis.

A Text-Book of Anatomy for Nurses. By William Gay Christian, M. D. With 34 original illustrations, 5 of which are in colors. 1917. 12°. 222 pages. C. V. Mosby Company, St. Louis.

Fiske Fund Prize Essay No. LVII. The Rôle of the Teeth and Tonsils in the Causation of Arthritis. By Dr. Joseph F. Hawkins. 1917. 8°. 29 pages. Snow & Farnham Co., Providence, R. I.

The Child in Health and Illness. By Carl G. Leo-Wolf, M. D. Illustrated. 1917. 8°. 297 pages. George H. Doran Company, New York.

Royal Academy of Medicine in Ireland. Transactions. Volume XXXV. Edited by J. Alfred Scott, M. A., M. D., F. R. C. S. I. 1917. 8°. 292 pages. John Falconer, Dublin.

The Institutional Care of the Insane in the United States and Canada. By Henry M. Hurd, William F. Drewry, Richard Dewey, Charles W. Pilgrim, G. Alder Blumer and T. J. W. Burgess. Edited by Henry M. Hurd, M. D., LL. D. Volumes III and IV. 1916-1917. 8°. 880 pages; 652 pages. The Johns Hopkins Press, Baltimore, Md.

Clinical Cardiology. By Selian Neuhof, B. S., M. D. 1917. 8°. 302 pages. The Macmillan Company, New York.

American Ophthalmological Society. Transactions. Volume XV. 1917. 8°. 332 pages. American Ophthalmological Society, Philadelphia.

The Prescription, Therapeutically, Pharmaceutically, Grammatically and Historically Considered. By Otto A. Wall, Ph. G., M. D. Fourth and revised edition. 1917. 8°. 274 pages. C. V. Mosby Company, St. Louis.

Diseases of the Skin. By Richard L. Sutton, M. D. With 833 illustrations and 8 colored plates. Second edition, revised and enlarged. 1917. 8°. 1021 pages. C. V. Mosby Company, St. Louis.

Metropolitan Asylums Board. Annual Report for the year 1916. (19th year of issue.) 1917. 8°. 55 pages. Sylvan Grove, London.

Human Physiology. By Professor Luigi Luciani. Translated by Frances A. Welby, with a preface by J. N. Langley, F. R. S. In five volumes. Vol. IV. Edited by Gordon M. Holmes, M. D. *The Sense Organs.* 1917. 8°. 519 pages. Macmillan & Co., 1917.

The School Nurse. A Survey of the Duties and Responsibilities of the Nurse in the Maintenance of Health and Physical Perfection and the Prevention of Disease among School Children. By Lina Rogers Struthers, R. N. With 24 illustrations. 1917. 12°. 293 pages. G. P. Putnam's Sons, New York and London.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. By leading members of the medical profession throughout the world. Edited by H. R. M. Landis, M. D. Volume III, Twenty-seventh series. 1917. 8°. 306 pages. J. B. Lippincott, Philadelphia and London.

A Reference Handbook of the Medical Sciences. Embracing the Entire Range of Scientific and Practical Medicine and Allied Science. By various writers. First and second editions edited by Albert H. Buck, M. D. Third edition completely revised and rewritten. Edited by Thomas Lathrop Stedman, A. M., M. D. Complete in eight volumes. Volume 8. Illustrated by numerous chromolithographs and 337 half tone and wood engravings. 1917. 4°. 782 pages. William Wood & Co., New York.

The Principles of Acidosis and Clinical Methods for its Study. By Andrew Watson Sellards. 1917. 8°. 117 pages. Harvard University Press, Cambridge.

St. Luke's Hospital. Medical and Surgical Reports. Volume IV. 1917. 8°. 404 pages. The Press Publishing Co., East Stroudsburg, Pa.

A Treatise on Regional Surgery. By various authors. Edited by John Fairbairn Binnie, A. M., C. M., F. A. C. S. Volume II. With 213 illustrations. 1917. 8°. 656 pages. P. Blakiston's Son & Co., Philadelphia.

Radium Therapy in Cancer at the Memorial Hospital, New York. (First Report: 1915-1916.) By Henry H. Janeway, M. D. With the discussion of treatment of cancer of the bladder and prostate, by Benjamin S. Barringer, M. D., and an introduction upon the physics of radium, by Gioacchino Failla, R. E., A. M. 1917. 8°. 242 pages. Paul B. Hoeber, New York.

Recollections of a New York Surgeon. By Arpad G. Gerster, M. D. 1917. 8°. 347 pages. Paul B. Hoeber, New York.

White and Martin's Genito-Urinary Surgery and Venereal Diseases. By Edward Martin, A. M., M. D., F. A. C. S. Benjamin A. Thomas, A. M., M. D., F. A. C. S., and Stirling W. Moorhead, M. D., F. A. C. S. Illustrated with 422 engravings and 21 colored plates. Tenth edition. 1917. 8°. 929 pages. J. B. Lippincott Company, Philadelphia and London.

Technique of Operations on the Bones, Joints, Muscles and Tendons. By Robert Soutter, A. B., M. D. (Harvard.) 1917. 8°. 350 pages. Macmillan Company, New York.

Publications of the South African Institute for Medical Research. Edited by W. Watkins-Pitchford, M. D. (Lond.) No. IX. (1) *Lysed Bacterial Serum.* (2) *Further Observations on Plantication.* (3) *A Note on Phagocytosis in the Absence of Serum.* By A. R. Friel, M. D., F. R. C. S. I., and F. S. Lister, M. R. C. S., L. R. C. P. 1917. 4°. 14 pages. Printed by W. E. Hortor & Co., Ltd., Johannesburg.

Monographs of the Rockefeller Institute for Medical Research, No. 7. Acute Lobar Pneumonia, Prevention and Serum Treatment. By Oswald T. Avery, M. D.; H. T. Chickering, M. D.; Rufus Cole, M. D., and A. R. Dochez, M. D. 1917. 4°. 110 pages. The Rockefeller Institute for Medical Research, New York.

A Handbook on Antiseptics. By Henry Drysdale Dakin, D. Sc., F. L. C., F. R. S., and Edward Kellogg Dunham, M. D. 1917. 24°. 129 pages. Macmillan Company, New York.

Elements of Hygiene and Public Health. A Text-Book for Students and Practitioners of Medicine. By Charles Porter, M. D., M. R. C. P. (Edin.) With 98 illustrations. 1917. 12°. 411 pages. Henry Frowde; Hodder & Stoughton, London.

Elements of Field Hygiene and Sanitation. By Joseph H. Ford, B. S., A. M., M. D. Approved for publication by the Surgeon General U. S. Army. 1917. 248 pages. P. Blakiston's Son & Co., Philadelphia.

Diseases of Women. By Harry Sturgeon Crossen, M. D., F. A. C. S. Fourth edition, revised and enlarged. With 800 engravings. 1917. 8°. 1160 pages. C. V. Mosby Company, St. Louis.

The Treatment of Infected Wounds. By A. Carrel and G. Dehelly. Translation by Herbert Child, Captain R. A. M. C. (Ty.) With introduction by Sir Anthony A. Bowlby, K. C. M. G., K. C. V. O., F. R. C. S. 1917. 12°. 238 pages. Paul B. Hoeber, New York.

Medical Diagnosis. For the Student and Practitioner. By Charles Lyman Greene, M. D. With 14 colored plates and 548 other illustrations. 1917. 8°. 1302 pages. P. Blakiston's Son & Co., Philadelphia.

The Destiny of the American Surgical Association. By J. Ewing Mears, M. D., LL. D. Reprinted from the Transactions of the Association, Vol. XXXV, 1917. 1917. 8°. 12 pages. Wm. J. Dornan, Philadelphia.

Royal College of Surgeons of England. Calendar. 1917. 8°. 407 pages. Taylor & Francis, London.

Impotence and Sterility. With Aberrations of the Sexual Function and Sex-Gland Implantation. By G. Frank Lydston, M. D., D. C. L. 1917. 8°. 333 pages. The Riverton Press, Chicago.

An Introduction to the History of Medicine. With Medical Chronology, Suggestions for Study and Bibliographic Data. By Fielding H. Garrison. Second edition, revised and enlarged. 1917. 8°. 905 pages. W. B. Saunders Company, Philadelphia and London.

A Manual of Anatomy. By Henry Erdmann Radasch, M. Sc., M. D. With 329 illustrations. 1917. 8°. 489 pages. W. B. Saunders Company, Philadelphia and London.

Studies from the Rockefeller Institute for Medical Research. Reprints. Volume XXVII. 1917. 8°. 559 pages. The Rockefeller Institute for Medical Research, New York.

A Text-Book of War Nursing. By Violetta Thurstan. 1917. 12°. 227 pages. G. P. Putnam's Sons, London and New York.

A Practical Dietary Computer. By Amy Elizabeth Pope. 1917. 12°. 156 pages. G. P. Putnam's Sons, New York and London.

The Principles of Mental Hygiene. By William A. White, M. D. With an introduction by Smith Ely Jellife, M. D., Ph. D. 1917. 12°. 323 pages. The Macmillan Company, New York.

Talks on Obstetrics. By Rae Thornton LaVake. 1917. 12°. 157 pages. C. V. Mosby Company, St. Louis.

An Intermediate Text-Book of Physiological Chemistry with Experiments. By C. J. V. Pettibone, Ph. D. 1917. 80. 328 pages. C. V. Mosby Company, St. Louis.

Physical Diagnosis. By W. D. Rose, M. D. 294 illustrations. 1917. 8°. 499 pages. C. V. Mosby Company, St. Louis.

Surgery and Diseases of the Mouth and Jaws. A Practical Treatise on the Surgery and Diseases of the Mouth and Allied Structures. By Vilray Papin Blair, A. M., M. D., F. A. C. S. Third edition, revised so as to incorporate the latest war data concerning gunshot injuries of the face and jaws. With 460 illustrations. 1917. 8°. 733 pages. C. V. Mosby Company, St. Louis.

The Medical Association of the State of Alabama. Transactions. 1917. 8°. 632 pages. The Brown Printing Company, Montgomery, Ala.

NEW PUBLICATIONS.

The following six monographs:

Free Thrombi and Ball-Thrombi in the Heart. By J. H. Hewitt, M. D. 82 pages. Price, $1.00.

Benzol as a Leucotoxin. By Laurence Selling, M. D. 60 pages. Price, $1.00.

Primary Carcinoma of the Liver. By M. C. Winternitz, M. D. 42 pages. Price, 75 cents.

The Statistical Experience Data of The Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By Frederick L. Hoffman, LL.D., F.S.S. 161 pages. Price, $2.00.

The Origin and Development of the Lymphatic System. By Florence R. Sabin. 94 pages. Price, $2.00.

The Nuclei Tuberis Laterales and the So-called Ganglion Opticum Basale. By Edward F. Malone, M. D. Price, $1.50.

are now on sale by The Johns Hopkins Press, Baltimore. Other monographs will appear from time to time.

The Johns Hopkins Hospital Bulletins are issued monthly. They are printed by the LORD BALTIMORE PRESS, Baltimore. Subscriptions, $3.00 a year (foreign postage, 50 cents), may be addressed to the publishers, THE JOHNS HOPKINS PRESS, BALTIMORE; single copies will be sent by mail for fifty cents each. Single copies may also be procured from the BALTIMORE NEWS CO., Baltimore.